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DEPARTMENT OF REVIEWS

... Journal will make an especial feature of the review of monographs and books bearing ... field of Internal Medicine. Authors and publishers wishing to subject such material ... consideration of review should send it to the editor. While obviously impossible to make ... reviews of all material, an acknowledgment of all matter sent will be made in the ... department of reviews.

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The Pathogenesis and Treatment of Dyspnea in the Light of Recent Experiments*

By C. S. Danzer, M.D., F.A.C.P., *Instructor in Medicine, Columbia University, New York*

THE treatment of dyspnea is important not only because of its intensely disagreeable nature but because this symptom is indicative of a profound physiological disturbance in the supply of oxygen to the tissues. Furthermore in applying suitable therapeutic measures for the relief of this symptom, a favorable influence is incidentally exerted on certain very vital mechanisms.

For convenience we may divide the dyspneas into two general groups:—1—The spontaneous paroxysmal attacks, 2—The more insidious types brought on by effort or by the horizontal posture (orthopnea).

Under the first heading we wish to discuss three subgroups — *Cardiac Asthma — Bulbar Arteriosclerotic Dyspnea*—and *Broncho-spastic Dyspnea*. The second group comprises that variety most commonly seen in heart failure. It manifests itself as breathlessness on exertion and is followed later by orthopnea.

We hope to show that these forms of dyspnea can be separated, and that each has its own mechanism and appropriate form of treatment.

Cardiac Asthma — This form of breathlessness, which sets in suddenly, usually when the individual is at rest, frequently awakening him from deep sleep, compels him to sit up in bed and pant for breath. The associated symptoms vary considerably in different cases. The pulse may be feeble and irregular or fairly strong and not very rapid. Râles (squeaking or bubbling) in the lungs may be present or absent; in some cases the attack may go on to pulmonary edema. Cough may be present and at times there is expectoration of a thin frothy sputum.

This wide variation in the character of the pulse and the degree of pulmonary congestion makes it possible that this symptom-complex is not an entity but embraces a variety of different conditions having a superficial resemblance.

Until quite recently the old Welch-Cohnheim theory of pulmonary edema, that of the left ventricular paralysis with strong right ventricular action, was offered as the explanation of cardiac asthma. The forcible pulse and the high blood pressure during

*Read before the American College of Physicians at the Annual Clinical Week, March 8, 1928, New Orleans, La.

the attack stand out as striking inconsistencies in this theory.

The work of Eppinger (1) and his associates and Wassermann (2) shed new light on this problem. The former showed very clearly that during attacks of cardiac asthma the blood velocity is greatly increased. The retarding or brake mechanism normally resident in the capillaries is lost so that the blood surges with great rapidity from the arteries to the veins and is then thrust with great force into the right heart and lungs. The terrific rate of speed with which the blood flows through the capillary network scarcely permits the arterial blood to lose some of its oxygen. The body cells suffer and the nerve cells in the medulla respond by producing dyspnea. A convenient descriptive name for this condition might be *centripetal engorgement asthma.*

A study of the effects of different drugs on the blood velocity shows that those drugs which definitely retard blood velocity are most useful in checking an attack of cardiac asthma. Morphine and pituitrin have such an effect.

In view of the importance of the rapid blood-flow in the genesis of these attacks, I have attempted to check the excessive venous return-flow to the heart by a simple mechanical procedure. Four blood pressure cuffs are applied to the extremities and inflated to a point well above venous pressure. For convenience the diastolic pressure is taken as the measure of the constricting force to be applied around the extremities. This is applied for 10 or 12 minutes and then the cuffs are very gradually deflated. The latter fact is of great importance if we are to avoid overtaxing a strained heart by the gush of blood that would follow if the pressure were suddenly released. For this purpose we have constructed a simple apparatus called the "Venostat" which connects the four cuffs and permits the pressure in any or all of them to be regulated at will, by means of stop-cock arrangements.

When this is applied the blood pools in the four extremities thereby allowing the tissues of the limbs to receive their required oxygen quota, at the same time disembarrassing the over-burdened heart and allowing it during the 10-minute period to restore to some extent its lost tonus. When one recalls the uninterrupted work of the heart during a lifetime, it seems possible that the reduction of the cardiac load for even as short a time as this may be effective. The relief that patients get from this procedure is very gratifying. In three or four minutes the breathing becomes less labored and slower, the patients exclaim that a weight has been lifted from the chest. Sonorous râles previously present diminish or even disappear for the time being, the right cardiac border recedes slightly and the patient loses his strained facial expression because of the relief of his dyspnea.

There seems to be a little obscurity concerning the manner by which a therapeutic procedure, which slows the blood velocity, acts in cardiac asthma. I should like to advance the following hypothesis. It is based on the correlation between the velocity and pressure in the veins and the cerebro-spinal pressure. The fact that

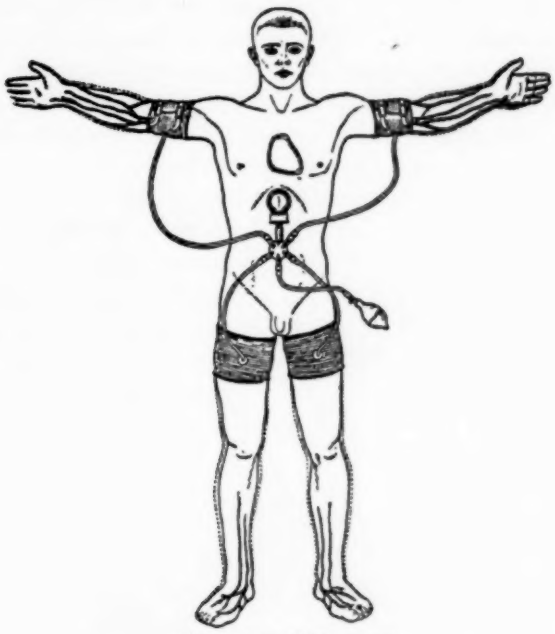

FIGURE 1—VENOSTAT

these attacks usually come during sleep (and the recent observation coming from Foster Kennedy's Clinic at Bellevue Hospital to the effect that intracranial pressure rises during sleep), has suggested the thought that a cranial hypertension may be a factor in the production of the attack. The flooding of the vena cava prevents easy emptying of the cranial venous sinuses thereby causing a rise in pressure which is then transmitted to the cerebro-spinal canal.

By our mechanical method of withholding a volume of blood from the heart, the pressure in the vena cava and cerebral venous sinuses must fall and likewise the cerebro-spinal pressure. One of the important coefficients in the production of the attack of cardiac asthma having been removed, the vicious cycle would be broken. That the spinal pressure actually falls after the venous compression in the extremities can be seen from the following—

M.K. — Age—44 — Diagnosis — Tabes Dorsalis

	Spinal Pressure	
Before	10 m.m. Hg.	Venostasis has produced a drop in spinal pressure of 30%.
Applied Venostat	7 "	
After removal of Venostat	12 "	

We have stated at the outset that cardiac asthma may be elicited by different mechanisms. A significant suggestion recently made by Wassermann is that such an attack may be an abor-abortive or forme fruste of pulmonary edema. The early occurrence

of the tachycardia and the maintenance of an increased arterial blood pressure during the attack suggested the possibility of a reflex mechanism stimulating the sympathetic nervous system as the initial disturbance. If this hypothesis be correct an antagonistic reflex might inhibit the latter and so check the attack. The "Vagus Pressure" reflex, more correctly called the Carotid Sinus reflex by Hering (4) accomplished this very thing. The afferent arc of this reflex is the descending branch of the glosso-pharyngeal nerve and the efferent part, the motor fibres of the vagi and the depressor vasomotor fibers.

The results of this procedure as reported by Wassermann are startling in that this severe clinical condition is checked very quickly. The compression must be made over a localized spot in the neck in order to elicit the vagus reflex. The illustration (Fig. 2) is presented in order to clarify the technique of this procedure. The point to be compressed with the finger (Point 1 in Fig. 2) corresponds to the bifurcation of the common carotid artery. The right side is usually more sensitive in eliciting this reaction than the left.

Bulbar Arteriosclerotic Dyspnea—As the study of the effect of venostasis was extended to other types of dyspneic paroxysms, another variety, clinically similar to cardiac asthma, was found, which was not benefited, even aggravated by this method of treatment. Such patients show either the characteristic Cheyne-Stokes or the so-called undulating respiration (Wogende Atmung) in which periods of deep breathing alternate with those of shallow breathing. The patient feels breathless. There is often evidence of arteriosclerosis or hypertension. This condition has been called "Paroxysmal Hypertension Dyspnea" by Pal, "Renal Asthma" by Romberg.

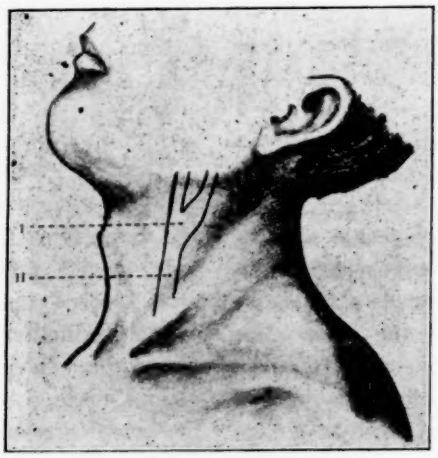

FIGURE 2—(After Hering)

In other cases the breathing is deep, more frequent, though regular and only after the respiratory center is depressed by a hypodermic injection of morphine (gr. ¼) does it take on the Cheyne-Stokes character. With the onset of the latter the sensation of air hunger is much diminished.

The mechanism of Cheyne-Stokes breathing becomes clearer in the light of the following experiments:—

Intravenous injections of 1 c.c. of adrenalin (.02%) elicits this type of respiration in rabbits and cats (5).

Amyl nitrite (6) restores Cheyne-Stokes back to normal breathing. It seems possible that arteriospastic conditions of the medulla are responsible for this respiratory disorder.

It is corroborated by the observation of areas of softening in the medulla at post-mortem examinations of cases showing this type of breathing.

The point which we wish to emphasize is that the Cheyne-Stokes breathing may be masked by a hyperpneic reaction if the bulbar ischemia be very pronounced. In this case the excitation of the respiratory center may be removed by a hypodermic injection of morphine, thereby exposing the periodic form of respiration.

Since it appears to be an arteriospastic condition, the purin group of drugs seems indicated. Actually we have found that Euphyllin (a theophyllin derivative, which can be given intravenously) will check the Cheyne-Stokes breathing within a fraction of a minute.

For continuous medication Diuretin in 10 grain doses combined with 1-10th grain morphine sulphate t.i.d., and supported in some cases by small doses of digitalis, has given very satisfactory results. The Diuretin and Euphyllin have a similar vasodilator effect.

Broncho-Spastic Dyspnea — The prototype of this form of breathing is seen in the attack of bronchial asthma. It is, however, by no means confined to the latter condition. Thus simple attacks of acute or chronic bronchitis may show it or it may be present during the course of a pneumonia.

To illustrate: A 59 year old man with a severe pneumonia with delirium, cyanosis, dyspnea, (orthopnea) and stupor was seen. It appeared to be a case of continuous dyspnea (to be described below) and venostasis was thought advisable. It was applied with marked improvement in his dyspnea, mental state and pulse. This state of well being was only temporary. After several days the dyspnea recurred. The venostat was again applied with great confidence but this time there was no improvement, the man was even made worse. On closer examination it was possible to explain these results. His dyspnea was expiratory in character, was associated with suppressed vesicular breath sounds such as occur in bronchial stenosis in which condition venostasis is ineffectual. This explains the failure to relieve the dyspnea .

Fortunately there are a number of pharmacological reactions which help to separate this form from other forms of dyspnea. I am referring to the favorable effects of epinephrin, ephedrin, atropine, large doses of caffeine or sodium iodide on this type of

dyspnea. The presence of eosinophiles in the sputum also helps to recognize broncho-spastic dyspnea.

I have on several occasions seen attacks of genuine cardiac asthma taken to be bronchial asthma because of the wheezing respiration, the presence of rhonchi and the associated emphysema. These findings, however, may complicate cases of cardiac asthma. They are not in themselves sufficiently characteristic to diagnose bronchial asthma. The poor response to adrenalin and the beneficial effects from venostasis favor the diagnosis of cardiac asthma, thereby differentiating these two conditions at the same time indicating the proper course of treatment. This is a point of considerable practical value.

FIGURE 3. (After Hofbauer)

e—expiration
i—inspiration

Decompensated
Compensated after Digitalis

Continuous Dyspnea, Orthopnea and the Dyspnea Effort

A. *Physical Factor*—

For a long time Von Basch's theory of pulmonary rigidity consequent upon the engorgement of the interalveolar capillaries was the accepted one. The expansile power of the lung was said to be reduced. The recent studies of Peabody (7) in which the reduced vital capacity found in decompensated cardiacs were advanced to revive this theory. That this inference is not correct may be seen from the respiratory tracings during decompensation and compensation.

It can be seen that during heart failure the breathing is much deeper and each phase of respiration is quicker than during compensation. This could hardly have been the case if the expansion of the lung had been reduced during decompensation.

Peabody's work on vital capacity in cases of heart failure is correct. The reduced vital capacity, however, is not because the lungs cannot expand sufficiently. It is due to another disturbed mechanism of respiration.

If one looks at the profile of a person who is breathing deeply one can see that as the chest is lifted during inspiration, the abdominal wall (if in harmony with the descent of the diaphragm) moves forward. In decompensated cardiacs there is frequently a paradoxical effect in that there is no inspiratory protrusion of the abdomen. (See Fig. 4.) The abdominal wall protrudes instead of retracts dur-

ing expiration. Wenkebach, Eppinger and Hofbauer (8) have shown this expiratory pump mechanism to be very important as an accessory factor in the circulation. Under this condition of reversed expiratory effect the return flow of blood from the lower extremities and liver is interfered with. The result is an edema of the legs, a congestion of the liver, and a reduction in vital capacity. The latter is due to the disturbance in expiration which makes it impossible to expel completely the air content of the lungs especially the reserve air.

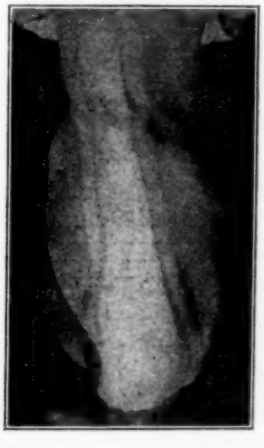

FIGURE 4—(After Hofbauer)

The therapeutic suggestion from these considerations is, to treat such cases by systematic breathing exercises so that the patient will properly synchronize his abdominal with his chest movements. By this means Hofbauer has achieved some brilliant results not only in relieving the dyspnea but also in reducing the edema.

B. *Chemical Factor.*

The next factor in the treatment of this type of dyspnea, especially that accompanying exertion, is the chemical reaction of the blood during work.

Our early results with the use of the venostat in treating cardiac asthma were so satisfactory that we attempted to treat other bedridden patients with orthopnea, cough and edema by this method. The patients were put on a limited fluid diet, no drugs were given and the veins in the extremities were compressed for 10 minutes at intervals of two hours. We were agreeably surprised to find that the edema lessened, the urine output increased and the dyspnea was favorably influenced.

These results were not very comprehensible at first, since it seemed that the venostatic method would be applicable only in conditions where the blood velocity was increased. Up to that time cardiac asthma was practically the only condition in which this was known to occur.

In 1927, however, Eppinger (9) published his studies on the dynamics

of circulatory failure and showed that the increased blood velocity in cardiac asthma was due to a relative increase in the acidity of the blood. This was the result of a CO_2 retention. The existence of pulmonary complications (congestion or emphysema) was thought to interfere with the free diffusion of CO_2 through the pulmonary capillaries. A reduction in the irritability of the respiratory centre during sleep and the diminished CO_2 exhalation in shallow breathing were likewise considered operative in producing this effect.

He found that any condition which rendered the blood more acid, as the injection of acid into the veins of animals or allowing them to live in high concentrations of CO_2, caused cardiac enlargement due to an excessive venous return flow to the heart.

His next step was to show that in cases of cardiac decompensation there was a condition of latent acidosis. During exercise more lactic acid is produced in the blood than under normal conditions. It remains in the blood for an abnormally long time because the buffering mechanism in the blood and the tissues, by which this increase in lactic acid is neutralized, is defective. He found an increase in the lactic acid content of the blood from the radial artery in cases of heart failure.

Since acidosis is a factor in dyspnea it follows that the administration of alkali salts is indicated, as well as a diet tending towards the reduction in the acidity, namely, a lacto-vegetarian diet.

That benefits followed the use of lacto-vegetarian diet in dyspnea of cardiacs especially in the presence of arteriosclerosis was known for a long time. This concept has been ably championed by the great French clinician Huchard (10). Its mechanism at the time, however, was not clearly understood.

The last point that these researches clarified was the reason for marked dyspnea on exertion in certain functional diseases, e.g., "The Effort Syndrome" cases of the war period. These cases were frequently convalescents from the acute infectious diseases, influenza and pneumonia. It was striking to see their severe distress on mild exercise while patients with severe cardiovalvular defects carried on quite satisfactorily.

The explanation for this is given by the following experiments:—If a dog or rabbit be placed in an atmosphere containing 10% CO_2 he will develop an increased blood velocity and if allowed to remain in this atmosphere cardiac hypertrophy and enlargement will follow. The animals so treated, however, live on indefinitely because the buffering mechanism neutralizes the excess CO_2 taken up by the blood. If the animal be given an artificial infection (staphylococcus or streptococcus) it will be killed by exposure in the CO_2 in half an hour and present all the signs of severe acid poisoning (9). This shows that during the course of the infection the buffer mechanism had been impaired. This offers a chemical explanation for the clinical experience that infectious diseases frequently break down cardiac compensation. It also explains how

dyspnea on exertion may occur in cases without demonstrable heart disease in those whose buffering mechanism is defective, which was probably the case in the "Effort Syndrome" patients.

Finally, these considerations indicate that we may apply certain common therapeutic procedures in cardiac asthma, heart failure, Effort Syndrome and acute infectious diseases in general — namely — alkalinization by means of alkali salts and diet, and relieve the heart by checking the centripetal engorgement by the method of venostasis.

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Coronary Thrombosis*

By J. P. Anderson, M.D., *Cleveland Clinic, Cleveland, Ohio*

THAT coronary thrombosis presents a problem of differential diagnostic interest to the medical profession is evidenced by the many publications on the subject within recent years. A number of these articles have referred to the fact that coronary thrombosis may simulate gallbladder disease. Nevertheless, the possibility that abdominal symptoms may be due to coronary thrombosis is not being sufficiently borne in mind. For that reason, while I propose to present a general summary of our present knowledge of this disease, I wish to call attention to this point, in illustration of which a selected group of cases will be presented.

From the large series of cases reported from various places at the present time, the incidence of the disease may be estimated. Christian (1) alone reports a series of 71 cases; and White (2) reports two series, one of 62 and one of 27 cases, covering periods of five years and of six months respectively.

Let us not be misled, however, into thinking of coronary thrombosis as a condition diagnosed only in recent years. Reviewing the literature of the disease, we find that in 1896 George Dock (3) described four cases of coronary sclerosis and thrombosis which were verified by autopsies. One case apparently was due to rupture of an atheromatous abscess in the vessel wall, in the distal branches of which emboli of the substance were found.

De Lancey Rochester (4) reports having seen a case in 1893 in which the patient had frequent attacks of acute indigestion accompanied by severe epigastric pain requiring chloroform inhalations for relief. The final attack was terminated by rupture of the left ventricle.

Sir William Osler (5) reported a similar case in 1910. In his Lumleian Lectures on Angina Pectoris he presents the reports of some cases which were obviously coronary thrombosis. Osler recognized this differentiation, as he remarks of one case, "probably an attack associated with acute infarction of the ventricle as a pericardial friction was heard the next day." He also refers to several cases in which the patients had pain in the region of the liver accompanied by jaundice. One of these cases which was characterized by recurring attacks was diagnosed as gall stones; however, at operation no gall stones were found.

Much credit is due to Herrick (6) who in a report under the title of "Clinical Features of Sudden Obstruc-

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tion of the Coronary Arteries" emphasized the facts that this condition can be justifiably diagnosed without necroscopic verification and that the condition does not by any means always cause death. Following Herrick's report came that of F. M. Smith (7) whose thorough experimental study showed the electrocardiographic changes and clinical course after ligation of the branches of the coronary arteries in dogs.

In 1926 Louis Hamann (8) presented a very comprehensive and complete summary of coronary occlusion. Faulkner, Marble, and White (9) have reviewed the histories of thirty cases of coronary occlusion, comparing the symptoms with those in thirty cases of cholelithiasis.

All the signs and symptoms which are reported by these authors have been seen in the cases of the disease in our Clinic. Not all the classical signs have occurred in each case; and without the history some of the cases could not have been diagnosed .

A previous history of angina or dyspnea on exertion is of great importance, but on the other hand, its absence is of no significance, as sometimes individuals who have always enjoyed the best of health are suddenly stricken without a moment's warning.

The classical onset of the disease is similar to an attack of angina pectoris but is more severe, being accompanied by excruciating pain which requires the administration of morphine in large and repeated doses and at times chloroform inhalation before relief can be obtained.

The following two examples will illustrate the fact that many of the milder cases, as well as some which are more severe, may occur with little or no pain. In the first case the patient, while running for a car, developed a "shutting off" type of pain which made him slow down; however, he continued running, caught the car, and experienced an immediate cessation of pain upon being seated. Because this condition recurred on a similar occasion, the patient consulted a physician. Clinical findings showed an auricular fibrillation which has persisted ever since. The patient was only 34 years of age, had no rheumatic history, and had been accepted for life insurance shortly before. His heart rate did not respond to digitalis, and all electrocardiograms have shown an extremely low amplitude, so that we believe this condition can only have been caused by coronary thrombosis.

In the second case the patient, while driving home from his office, was seized with an intense dyspnea which caused him to lose the control of his car. He remembered everything except stopping his car, insisting that at no time did he experience any pain—simply an extreme shortness of breath. The electrocardiogram of this case showed inverted Ts in the first and second leads.

The classical location of the pain in coronary thrombosis is the same as that in angina—in the substernal area, and it is of the "boring pressure" type. This may be the only site of the pain, or it may be referred to the left shoulder or arm.

We have also had examples of pain in more unusual locations. One man had sudden acute pain between the

shoulders and in the lower jaw, accompanied by slight fever. Osteopathic treatments proved useless, the pain increasing until morphine was required for relief. Even after all the teeth of the patient had been removed, the pain still persisted. This condition, however, gradually cleared up with recurrence of pain only when the patient overexerted, the pain being usually associated with some pain in the substernal area. The electrocardiographic tracing showed delayed ventricular conduction, with notched Q, R, S and inverted Ts in lead I. He eventually died in a prolonged attack of anginal pain. I believe this man had thrombosis of one of the smaller coronary branches at the onset of his trouble and died as a result of thrombosis in another artery. However, as there was no autopsy, the diagnosis could not be verified.

Another patient had attacks which radiated to the back, thereby causing intense pain over all the cervical and thoracic dorsal sensory nerves. The characteristic pain in the substernal area with no radiation, however, to either arm or to the abdomen was found in this patient who was only 43 years of age.

Another patient because of pain in the right shoulder consulted the Orthopedic Department. At the time of examination the shoulder was found to be normal, but after pain had been present in the chest for two days, fever began to develop, accompanied by a sense of impending disaster. Four days later the patient was forced to stop work and died suddenly that night.

Physical signs:

1. An anxious, worried expression, as if fearful of impending disaster.

2. The skin becomes ashen in color, because of slight cyanosis underlying the paleness from shock, a condition which lasts long after the acute part of the attack is over.

3. There is no characteristic posture although the patients often have to sit up and lean forward for easier breathing. They sometimes hold themselves as if transfixed.

4. Wearn (10) has referred to a diffuse flushing early in the condition.

5. The pulse is weak and may be alternating regular or irregular, slow or fast, whereas in simple angina there is seldom any change.

6. The blood pressure shows a sudden drop in both systolic and diastolic pressures from a previous normal or markedly elevated level in contrast with that of angina. One case, however, showed the usual blood pressure reading of 185/120 mm. up to the time of the last record a few hours before death.

7. The temperature is normal or subnormal at first but rises about the end of the first day from 99° to 101° F., this elevation lasting from two to five days.

8. The respiration may be normal, shallow, rapid or forced or Cheyne-Stokes in type.

9. The precordial activity is feeble.

10. The borders of the heart are nearly always widened because of dilatation, the left border often extending to the anterior axilla.

11. The heart sounds are usually feeble, tic-tac or embryocardiac in character. A systolic murmur can be heard at the apex in about one half of the cases.

Phelps (11) has referred to a reduplication of the first apical sound as indicative of ventricular hypertrophy on the verge of failure. He states that within his knowledge all patients with this reduplication who have had major operations have died of progressive heart failure within one to three weeks after operation .

I thoroughly agree with him in regard to the risk of operative procedures but I believe the reduplication or "splitting" of the first sound is due to unequal contraction of the two ventricles, as I have found that such cases frequently show a bundle-branch block.

There are cases, however, where this does not seem to be the case, namely, those with acute hyperthyroidism in which a split first sound with gallop rhythm is fairly common. Likewise such cases do not show bundle-branch lesions and in operations they are not bad risks.

Pericardial-friction sounds are not always present but when found are almost pathognomonic. The absence of such sounds is explained in many cases by the facts that the infarcted area is frequently pyramidal with only the apex at the surface; that the infarct also may be so posterior that the friction is inaudible; and that friction sounds are evanescent and may be audible only for a few hours.

12. I shall refer to the rhythm under the electrocardiographic descriptions.

13. Pulmonary signs are nearly always present, the rapid edema and reduced resonance at the lung bases with the presence of numerous râles, sometimes suggesting pneumonia. I shall later refer to such a case. One of our cases showed such symptoms as hemoptysis and blood spitting, which are referred to in the literature.

14. Liver signs are often noted early, the marked congestion and distension causing great pain. I think this is readily understood if one recalls that many patients with mitral stenosis consult a doctor because of pain in the upper abdomen, the onset of which is never so sudden as in cases of coronary thrombosis.

15. Another heart-failure sign consists of gradually increasing edema, the findings depending on the time of examination.

In referring to heart failure signs, it should be understood that the coronary thrombosis may be in the left or right side of the heart and that the signs vary somewhat. With left-side damage, the lungs become affected quickly, other signs of failure being largely lacking; whereas with damage on the right side, the liver becomes engorged.

It must be remembered that the anterior descending ramus of the left coronary supplies part of the anterior surface of the right ventricle, so that it is possible to get right-side signs from a left coronary branch occlusion.

16. Signs of peripheral arteriosclerosis are not always present, though found in the majority of cases.

17. Anuria will be present during the period of markedly reduced blood

pressure. According to Cushing this reduced pressure may be below 40 mm. in dogs.

In one of our cases anuria lasted for twenty-four hours but the blood pressure was below 50 mm. about half the time.

18. Embolic phenomena are apt to occur when pieces of the thrombus from the endocardial surface break loose. Such symptoms were noted in only one of our cases, the embolus lodging in the right popliteal artery about thirty-six hours after the coronary occlusion had occurred.

19. The chief laboratory sign is leucocytosis which appears shortly after the onset and corresponds largely with the temperature, the figures varying from 10,000 to 24,000.

Urinalysis and blood chemistry findings depend largely on pre-existing conditions rather than on the present trouble, albumin and some casts being common. Bile is not often found in the urine, a helpful diagnostic point in patients with referred abdominal pain. It was found in only one of our cases and fortunately there was no suggestion of an abdominal lesion in this case.

Electrocardiographic Signs

The location of the infarcted area probably affects the electrocardiographic signs. A few cases which clinically were very clear-cut cases including presence of a pericardial friction rub, have shown no electrocardiographic abnormality other than inversion of Ps in lead III, one case showing inversion also in lead II.

Cardiac irregularities aside from extra systoles have been rather rare in our series. No cases of complete or partial auriculoventricular block have occurred at any time during which patients have been under observation. Only three cases of auricular fibrillation have been noted. The greater number of cases have shown changes in the ventricular complexes. In order to interpret these findings one must have a logical conception of the spread of excitation through the ventricles and the relation of this spread to the Q, R, S, T waves and intervals in the electrocardiogram.

Assuming that the Bundle of His with its ramifications is responsible for the spread of the excitation waves, I think the simplest explanation is that electrical activity is continuous from the onset of the Q to the completion of the T; that Q is indicative of activation of the upper septal region; that R and S indicate the summation of activity in the two ventricles; that the S-T interval indicates the isoelectric period when the greater mass of the ventricles has been activated and that the Ts indicate a period of final activation of the musculature at the base of the ventricles toward the arterial orifices.

An interruption of the usual spread by any overactive or inactive muscle will be shown by the electrocardiogram in the majority of cases. If there is a lesion, however, high up in the bundle, there will probably be little or no change because of the double blood supply to the main bundle, whereas lesions lower down produce changes in the right or left bundle with bundle-

branch lesions or perhaps complete branched bundle block.

Lesions in the peripheral ventricular wall will produce changes in the Ts usually in the form of inversion in one, two or three leads. Very little attention has been paid to an inversion of the T waves in lead III unless associated with changes in lead II or I.

Smith (7) in his article on electrocardiographic studies following ligation of the coronaries in dogs, reports that none of the five animals surviving ligation of the right coronary artery showed appreciable aberration of T waves, while in every case of obstruction of the left coronary artery definite aberration was shown.

This observation may explain a similar condition in one of our cases which clinically was a very definite case and yet showed in the electrocardiogram no change except low amplitude. The patient was not seen, however, until six months after his accident; thus we cannot say that there was no change at the time.

The fact that coronary thrombosis simulates the symptoms of other diseases, such as gall-bladder conditions, presents a problem of differential diagnosis. Two striking examples of such simulation are reported by Levine and Trantor (12).

In the past four and one half years, we have made the diagnosis of coronary thrombosis 58 times, in 47 cases in men, in 11 in women. Twenty-seven patients are still living. Only two autopsy reports have been made. The question naturally arises as to the factors determining our diagnosis, seven of which may be briefly outlined:—

1. History of sudden onset of pain of anginal nature but more severe, lasting for a period of hours or days and requiring opiates for relief.

2. Sudden onset of dyspnea which incapacitates the patient, as in the case already mentioned.

3. Onset of pain or persistent recurrence of pain while the patient has been perfectly quiet.

One patient had eighteen recurrences of pain in twenty-four hours, partially relieved by nitrites, and he died the following day. This is the case mentioned previously in which the patient had the pain referred to the cervical and thoracic segments.

4. Electrocardiographic findings of a complete or partial bundle branch block, if there has been a previous normal electrocardiographic tracing. A complete bundle branch block without anginal pain, in the absence of other explainable cause, has been considered as probably diagnostic of this thrombotic condition. Two cases of syphilis with bundle lesions have not been included here, as the lesions may have been due to gummata.

5. Slight changes in the Q, R, S complexes with inversion of T waves in two or more leads in the absence of medication affecting T waves, especially if this finding has been persistent in more than one examination. Altered T waves alone have not been considered sufficient diagnostic evidence; neither has any type of irregularity nor altered P waves.

The death of the patient during a prolonged anginal seizure has been found to be due to coronary thrombosis in one or two questionable cases.

6. The presence of a pericardial friction rub in a questionable case has been considered definitely confirmatory evidence, whether or not any electrocardiographic tracing was obtained.

Case Reports

Case I: The patient was a man 71 years of age, a floor walker by profession, who entered the Clinic on June 2, 1927. His father died at the age of 76, of kidney trouble; his mother died at 55, of heart trouble. He had two brothers and two sisters, all of whom were living and well. In May, 1926, he had had nosebleed and had been told that he had high blood pressure.

At the time when we saw him, he had come to consult Dr. W. E. Lower, to find out whether or not he needed a gall-bladder operation. He had been quite well until three years before. At that time he had been about to take a street car when he had a premonition of illness and went into a drug store. There he suffered excruciating pain in the left lower quadrant of the abdomen, which quickly radiated to the right lower abdomen, then to the right upper abdomen, where it persisted. There was also pain in the substernal and clavicular areas.

The doctor who was called pronounced it gallstone colic and said he would have to be operated on at once. This the patient refused to permit until he had other consultation, and he was moved to his home. His family doctor pronounced the condition pleuropneumonia. He was sick for eight weeks and had to be kept under the influence of morphine during the first week. The patient said his fever was never so high as one would expect it to be in pneumonia.

Examination gave the following findings: A pale, slightly ashen appearance; arteries thickened++, retinal arteries+++; B.P. 210/110; P. 64. The heart was moderately enlarged, extending beyond the left nipple line and the action was grossly irregular because of extrasystoles. There were no signs of failure, no areas of tenderness in the abdomen. An electrocardiogram showed a marked left ventricular preponderance, with inverted Ts in all leads and inverted Ps in lead III. There were numerous extrasystoles. The urine, blood counts and blood sugar were normal. Basal metabolic rate, estimated for scientific purposes,—1 per cent.

Our impression was that he was suffering from arteriosclerosis and that his former illness had been coronary thrombosis instead of pneumonia. He was kept at relative rest for two months and was given nitroglycerin. He then felt so much better that he was allowed to return to work, his blood pressure being 190/110. He remained at work for four months. Then one day he had to walk up seven flights of stairs and since that time he has had to stop work and has been unable to exert himself much without having an attack of substernal pain.

This case illustrates the fact that coronary thrombosis may be mistaken for either of two conditions. The first physician saw the patient at a time when he was having acute pain and tenderness in the right upper quadrant of the abdomen and he attributed it to gallstone colic, when in all probability it was due to engorgement of the liver with stretching of Glisson's capsule. When the second doctor saw him there must have been many râles in the lungs, which were considered to be due to pneumonia instead of the pulmonary edema.

In this case there was evidence of failure, first in the right side of the heart and later in the left side, and it is probable that there was thrombosis of the anterior descending ramus of the left coronary artery, which supplies the lower anterior wall of both the left and right ventricles.

Case II: The patient was a man 68 years of age, who came to Dr. Crile on June 9, 1926 for cholecystectomy. His father died of cardiac trouble. The patient had had almost no previous illness except for mild rheumatism. In 1916 he had had one attack of some form of acute indigestion; and in August, 1923, two attacks of pain in the right subcostal area, partially relieved by elevating the leg and finally relieved by vomiting.

When he entered the Clinic the patient thought he was suffering from gall stones, as that diagnosis had been made previously. He had suffered from violent pain the night of December 12, 1925, with very severe pain in the right upper quadrant of the abdomen, attended by much vomiting. He was given morphin three times before he obtained relief, was unconscious for four days, and was very acutely ill for two weeks. Phlebitis developed in the right leg, and about a week later the same condition appeared in the other leg. This lasted about two or three weeks and was followed by bilateral pleurisy. It was the middle of February before the physician would risk moving him from the home of his relatives to his own home, which was only a few doors away, and he was confined to the house until the first of May. During the acute stage of his illness his temperature rose to 99.5° for several days, and remained at 101° for two days. B.P. 104/50 two weeks after the onset of the illness. No estimate had been recorded up to that time. There was no evidence of jaundice in the skin or urine. The pulse was usually good. White blood count, 22,000; polymorphonuclears, 89 per cent, three days after the onset of the illness. No precordial friction was noticed. The heart border was one inch beyond the nipple line.

At our examination, six months after the onset of the illness, his weight was 140 pounds—his average weight being 180—temperature 98.2, pulse 79, blood pressure 104/78. An ashen color and arcus senilis were observed. The heart borders were 3 cm. and 10 cm. respectively, beyond the midsternal line. The sounds were very distant and of poor quality. There was a faint systolic murmur at the apex; the aortic second sound was slightly accentuated; there were no râles at the lung bases; the peripheral arteries were moderately thickened; the legs showed practically no edema.

The electrocardiographic tracing showed nothing abnormal except reduced amplitude; the waves were normal. A gastro-intestinal series was essentially normal. The duodenal bulb was slightly deformed but there was no suggestion of an ulcer A cholecystogram was made and no gall-bladder shadow could be seen 15, 19 or 23 hours after the ingestion of the dye. In the bromosulphthalein test no dye was recovered in 30 minutes.

This was considered to be a case of coronary thrombosis and the patient was allowed gradually to increase his exercise until he was going about considerably. He then returned to his home and has had biyearly examinations ever since. All electrocardiograms have shown normal waves. The patient was last heard from in February, 1928, and at that time he was still feeling well and was planning to make a trip to Europe this summer.

In this case the acute accident occurred while the patient was in another city. He was seen three times by a very competent consultant, and, so far as I am aware, coronary thrombosis was not considered, the condition being attributed to gallbladder disease with gallstone colic.

The cholecystogram gave evidence of disease of the gallbladder while the electrocardiograms have all shown normal tracings except for low amplitude. Nevertheless, I cannot conceive of any gallbladder condition which could produce a clinical course such as the one in this case—the very sudden onset with excruciating pain, requiring that the patient be kept under morphia for a week and unconscious for the first four days; the heart border one inch beyond the nipple line, with weak sounds and the blood pressure 104/50 about two weeks after the onset; no signs of jaundice in the skin, stools or urine at the time; the temperature rising to 101° and the white blood-cell count to 22,000. Add to this the fact that it was two months before his medical advisers would permit the patient to be moved a few doors to his own home and that it was six months before he set foot outside his house. Taking all these facts into consideration, it is very unlikely that gallbladder disease was solely responsible for his trouble. Both coronary thrombosis and cholecystitis may have been present, the former attacks being due to the gallbladder trouble and the latter attacks

to thrombosis. In any event, I think he owes his good condition to the fact that he had complete rest for six months and intensive rest for the next six months. No electrocardiograms were made until six months after the onset of the illness. The negative findings can be explained, I think, on the basis of Smith's work—he found that in no case did ligature of the right coronary artery cause inversion of the Ts—and of course it is quite possible to have an extensive lesion with no disturbance of the bundle conduction.

Case III: The patient was a woman 55 years of age. Her husband has tabes but her Wassermann and Kahn tests have twice given normal results. She was first seen in May, 1925. Her chief complaint was of attacks of choking pain in the throat and of epigastric distress, which she has had since 1921. At that time she had a hypertension of 240.

The pain in the throat came upon exertion and was relieved by rest. When the pain was bad, it also came in the jaw and the patient felt as though her teeth were being pulled. The pain occurred under the sternum and radiated up the left side of the head and down each arm. The pain in the chest and neck was of the "'clutching" type.

The examination of the heart gave essentially normal findings and the electrocardiographic tracing was normal. There was persistent tenderness in the region of the gallbladder. Plain gallbladder plates and plates made with barium showed no evidence of gallbladder disease, so we attributed the condition chiefly to angina.

In January, 1926, the patient's condition became so bad that she was admitted to the hospital. The attacks seemed definitely to be aggravated by food but there was no more tenderness in the abdomen than had been present all the time.

The patient was having pain more than half the time and insisted that something be done, so I requested Dr. C. E. Locke to perform a cervical sympathectomy. The superior middle and inferior cervical ganglia were removed *in toto*, and this was followed by a typical Bernard-Horner syndrome. The patient's condition seemed somewhat improved but she still had pain and the pain went also down the left arm. In September, 1926, while I was on my vacation, acute pain developed in her abdomen, radiating to the right subscapular area. This was different from any attack she had ever had before. Dr. C. L. Hartsock had her enter the hospital, where a cholecystogram was made. This indicated a diseased condition of the gallbladder, so operation was performed by Dr. T. E. Jones. Acute cholecystitis with a small abscess was found.

Following the operation the patient had relief from the angina for nearly a year. It recurred, however, with sudden pain, and an electrocardiogram made shortly afterwards showed inverted T waves in lead I. At the present time her electrocardiographic tracing is again normal. However, she still has anginal attacks, still has pain in the left arm, cannot walk more than 200 feet without having to stop because of a spasm, and still uses some nitroglycerin. In spite of all this she is taking care of a 15-room boarding house and does her own work except the scrubbing.

This case is chiefly one of angina but since, after an attack of severe pain, inverted Ts waves showed in the electrocardiogram, it is possible that a small vessel was occluded. It is a good example of a case in which two pathological conditions are present and of the confusion that may arise as the result. It is also an interesting fact that the anginal attacks and the pain referred down the left arm still recur after a complete left cervical sympathectomy.

Case IV: This patient was a woman 62 years of age, who was seen on July 25, 1927.

Two nights before our examination, about ten o'clock in the evening, the patient was aware of pain through her chest which gradually grew worse until it seemed to run over her shoulders and down into her arms. It was equally severe in each arm. She thought that she must have taken cold. The pain must have lasted for at least several hours, for she thought of calling her daughter in the middle of the night, because she was suffering so severely. By morning it had entirely disappeared, she took a short walk during the day and felt

perfectly normal. When evening came, however, the pain returned so acutely that her daughter wanted to call a doctor. The patient did not think it necessary. She did not sleep all night and I was called at about 8:30 in the morning.

At the time of my visit the patient seemed to be having no discomfort. An examination of the heart revealed nothing. It did not seem much enlarged, there were no murmurs, no irregularity and no undue accentuations, and the sounds were clear. Percussion revealed no widening of the mediastinum. There was considerable tenderness in the region of the gallbladder on palpation.

This occurred after the patient in case III had been operated upon and while she was still free from anginal pain, so I considered the differential diagnosis between angina and coronary thrombosis or cholecystitis, which I might not have done otherwise. I gave the patient a hypodermic and asked her to stay strictly in bed. About 2:30 that afternoon I had a message that she was unconscious and she was dead when I reached her home. Autopsy revealed a ruptured heart, which appeared to be clear except for an area about 1.5 cm. in diameter around the posterior descending branch of the left coronary. This portion was bright red and showed under the microscope fragmentation of the muscle fibres without any necrotic reaction. There was a small thrombosis in the sclerosed vessel. The gallbladder was normal.

I think this case should be classified as one of coronary sclerosis and dissecting rupture of the coronary artery, the rupture of the intima occurring on the first night and rupture of the remaining layers on the second afternoon, with a secondary rupture of the cardiac muscle.

Case V: This patient was a physician, 52 years of age, who was first seen on November 25, 1921. The family history was negative for tuberculosis or heart trouble. His father died from nephritis and his mother from liver trouble. The patient had had tonsillitis in childhood and pneumonia in 1902. His left kidney had been removed five years before and there had been a question of adenoma. He used no alcohol but smoked from two to four cigars a day.

The patient complained of a feeling of oppression and constriction over the precordium, which became very marked at times on exertion. He also had some trouble with gas on the stomach. One week before, after two heavy meals, he had had such severe pain in the epigastrium that at 4 A. M. he had to have a hypodermic of ¼ gr. of morphin and 2½ gr. by mouth. The opiate caused vomiting. He had had a degree of temperature since that time. There was no shortness of breath.

On examination the chest expansion was found to be poor but equal on both sides; the heart was not enlarged; there were no murmurs; the aortic second sound was tympanitic, the pulse was 72; B.P. 135/75; no arterial thickening; the abdomen showed a scar from the nephrectomy and there was some tenderness under the right costal margin.

The patient was not seen again until October 21, 1927, when Dr. Phillips saw him in consultation at his home.

On the preceding night he had been seized with a very severe pain in the epigastrium, with some nausea and vomiting, although this was not a marked feature. He at once became extremely pale and went into a condition of collapse. He was seen by a surgeon, who thought that he had a perforated gastric ulcer, but his condition was so serious that operation was not advised. He was also seen by Dr. Weller, who saw at once that the condition was cardiac in origin. The heart was considerably dilated to the left and to the right. The heart sounds were very faint. The blood pressure could not be estimated because it was so low. The heart was about 160. It was impossible to count the pulse, which was faintly perceptible. There were some changes at the base of the right lung and there was some enlargement of the liver. Morphin was given in moderate doses of ¼ gr. every four to six hours during the day, and the patient's condition became somewhat improved.

On the following morning the patient complained of very severe pain in the left

calf and in a very short time the left foot became cold. This was evidently due to an embolus of the popliteal artery. On examination the patient's color was found to be somewhat pale, though not so markedly as would be expected. The heart was considerably dilated to the left, the left border reaching to the anterior axillary line, and it was also slightly dilated to the right. The heart sounds were extremely faint, no murmurs could be made out but there was a suggestion of a pericardial friction rub in the left fourth interspace. Some crackles were heard at the base of the right lung. The liver was slightly enlarged. The left foot was cold and there was some thickening in the middle of the calf, evidently at the point of closure of the vessel. The patient died within an hour. A diagnosis of coronary thrombosis and embolus of the popliteal artery was made.

Case VI: The patient was a man 51 years of age, who was referred to Dr. Crile to be considered for thyroidectomy. His chief complaint was of nervousness with air hunger. His heart had been irregular since 1925. His tonsils had been removed in January, 1927. He had recently had two short attacks of pain in the chest and at times had had to sit up in a chair at night because of dyspnea. His weight was 153, his average weight being 195. Heart and pulse rate 84, irregular, with auricular fibrillation. There was no palpable fullness of the thyroid. The heart borders were 4 and 12.5 cm. beyond the midsternal line. There was a systolic murmur at the apex and in the aortic area. The arteries were thickened. There were a few basal crackles, the liver was scarcely palpable. An electrocardiogram showed auricular fibrillation with left preponderance and Ts in the opposite direction and slurred. The first basal metabolism estimation gave +41; and a second, made three days later, +29 per cent. The charts showed a Cheyne-Stokes type of respiration. This case is chiefly one of coronary sclerosis, which has probably progressed to the point of occlusion of some small branches. Just why the basal metabolic rate should be so high I am not sure, but I believe it is associated with the sclerosis rather than caused by hyperthyroidism. We have seen an increased basal rate in some cases of paralysis agitans.

Case VII: The following case is reported to show that it is sometimes possible to rule out coronary thrombosis in making a differential diagnosis when there is a sudden attack of abdominal pain. In this case the pain was found to be caused by a gastric ulcer.

The patient was a man 65 years of age, who was sent to the hospital for a laparotomy because of sudden severe pain in the epigastrium. He had had one attack of vomiting without any blood. It was thought that he had a perforated gastric ulcer, but an examination was requested because of the possibility of coronary thrombosis. He had a previous history of gastric distress, his heart examination gave essentially negative results with no signs of failure, the electrocardiogram was normal and he had pain upon pressure and rigidity of the upper portion of the abdomen. The disturbance was reported to be not of cardiac origin and operation revealed a perforated ulcer at the pylorus.

Case VIII: The patient was a woman 57 years of age, who had a Riedel's lobe of the liver extending to a point below the umbilicus in the lateral right rectus area, and in 1926 she had a sudden attack of severe pain in the upper right quadrant of the abdomen. She was seen by a physician who had not seen her before and he reported that she had a greatly distended, acutely diseased gall-bladder. Operation was not performed because of her cardiac condition. It is possible that the patient had cholecystitis but it is also quite probable that the cardiac condition was responsible for the abdominal pain, for she is now having some anginal attacks.

Case IX: In 1921, a man about 60 years of age was admitted to the Toronto General Hospital in a prostrated and stuporous condition which, it was felt, was most probably due to uremia or to diabetic coma.

A history of the case obtained from his son revealed that the patient had been in

good health. That night he had started to eat a tomato and had choked on the juice. He gave a violent choking cough and then gasped because of excruciating pain in the chest and almost immediately became so prostrated that he was stuporous. He was brought immediately to the hospital.

The blood pressure could not be obtained, the patient's breath was negative for uremic or acitone odors, and the bladder contained no urine. Blood chemistry studies made on the following day gave negative results and about 16 hours after admission the patient died very suddenly.

Dissecting aneurysm of the aorta with rupture was suggested as the cause for this man's pain and death, and an autopsy revealed a dissecting aneurysm starting about one half inch above the aortic valve and perforating into the pericardial cavity about one inch higher up.

The pain apparently came with the rupture of the internal layer and the stretching of the outer layers of the aorta. I think it quite possible that that is what causes the pain in cases of coronary thrombosis rather than the presence of the clot with ischemia of the muscle.

Singer (13) has found in animal experiments that the arteries can be blocked with lycopodium spores and the animal evince no sign of pain. He also found that he could strip off the adventitial layer of the artery and ligate it suddenly, without producing any pain, but that if he pricked the adventitial layer with a needle, the animal would evince pain. Dr. Crile informs me also that the thyroid arteries are abundantly supplied with nerves and the patients evince pain when they are injured. From these findings it would seem that the pain is due to irritation of the nerves.

A thrombus does not always form after rupture of a calcified area of the aorta, and it is quite possible that the same is true in cases of rupture in the coronaries. The weakened wall may then become stretched with any sudden increase in the blood pressure such as that caused by exertion or excitement and relaxes with rest or following the administration of nitrites. Does this not seem a plausible explanation of the pain in angina?

The pain in coronary thrombosis is similar in character, location and radiation to that in angina, but it is usually more severe and much more prolonged; and it seems probable that the only difference is that in those cases in which thrombosis develops, a more extensive rupture of the vessel takes place with greater stretching. The pain is naturally more severe and prolonged, and it seems quite logical that nitrites should not relieve the pain in these cases; also it is quite conceivable that thrombosis may result from only a small internal fissure and be associated with very little pain.

It is impossible to know whether or not thrombosis will develop in a case in which an attack of moderately severe pain has occurred, but this possibility should always be considered, and the case should be treated as a case of thrombosis. The patient should have a long period of absolute rest in bed until it is felt that he is completely out of danger. We do not know how long it takes an ulcerated calcareous plaque to heal, but it is a wise policy to err on the side of safety and to allow a longer period than may, perhaps, be necessary.

How much of the abdominal pain is referred from the heart and how much is due to sudden engorgement

of the liver with stretching of Glisson's capsule is not certainly known, but, as I said above, patients with mitral stenosis quite frequently consult a physician because of abdominal pain and tenderness, and in those cases the failure is much less acute than in cases of thrombosis.

Conclusions

1. The precursor of coronary thrombosis is coronary sclerosis with calcareous plaque formation; that is followed by rupture of the plaque, escape of tissue fluid and subsequent thrombosis and cardiac infarction.

2. It seems probable that the pain is caused by the stretching of the vessel wall rather than by ischemia of the muscle.

3. The abdominal pain seems to be partially associated with sudden distension of Glisson's capsule.

4. A theory is offered for the etiology of angina pectoris—the superficial rupture of calcareous plaques without the escape of enough tissue fluid to produce thrombosis, but allowing a stretching of the artery wall.

5. Cardiac rupture may occur shortly after the onset of the thrombosis from rupture of the artery, or later from rupture of the infarcted muscle.

6. A great many patients survive the attack and recover to lead a fairly active life for many years.

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The Abuse of Digitalis*

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THERE is no member of the pharmacopeia more fascinating and intriguing than digitalis. The history of this drug is almost a medical epic. Its botanical name, Digitalis purpurea, was given to it by Fuchsius in 1542 because of the resemblance of its flowers to a finger or thimble and because of its purple color. Boerhaave regarded digitalis as a poison but other writers held that it was one of the native plants of England which should be considered a medicine of considerable virtue.

To that sterling old English physician, William Withering, the world owes a tremendous debt for his careful scientific investigation and clinical study of this remedy. Withering undertook the study of foxglove because he was informed of a secret remedy by which an old woman of Shropshire was frequently able to cure patients with dropsy who could obtain no relief from the leading medical men of the day. He began to use this drug in 1775 and after a period of ten years experience with digitalis wrote his masterly book. This in itself would indicate that he was not affected by "pruritus scribendi." He gives an account of 163 patients to whom he had given the drug and also published communications from other physicians who had used it. He states that he reported all patients to whom the drug was given, without selection, in order to prevent any unwarranted enthusiasm for this remedy. His case reports are concise, clear and graphic, and deal, strangely enough, almost exclusively with the diuretic effects of the drug and the disappearance of dropsy. While he observed the fact that digitalis slowed the pulse when given in large doses he did not associate this effect with any benefit the patient received, in fact he rather considered the slow pulse as a sign that the maximum dose of the drug had been given. The advice which he gave 143 years ago and which for many years was disregarded, is still sound "let the medicine be continued until it either acts on the kidneys, the stomack, the pulse or the bowels; let it be stopped upon the first appearance of any of these effects."

Could Withering observe today the enormous growth and prestige which

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this lusty infant has attained, I venture to say he would be amazed, and even perhaps somewhat apprehensive.

In spite of Withering's scholarly and lucid presentation of the subject the virtue of digitalis was practically ignored for over a hundred years.

Pratt after investigating this phase of digitalis and reviewing treatises on heart disease states that after going through Hope, Stokes, Latham and Walshe, as well as Austin Flint, found that they paid little or no attention to Withering's teachings and apparently did not know the great value of digitalis in cardiac failure.

He remarks however, that "Sir James MacKenzie, working over 100 years later, was the first clinician to demonstrate conclusively the correctness of Withering's instructions regarding the administration of digitalis."

While we must admit that this drug was ignored for a long period of time when it could have been readily used in medical treatment the situation has now been completely reversed and we find digitalis being put to every conceivable use so that untoward effects are a common observation. In certain disturbances of cardiac function there is no other known drug which is quite as effective. In the treatment of the congestive type of heart failure digitalis remains paramount. We must keep in mind, however, that digitalis is not the sovereign remedy for all affections of the heart, that its field is strictly limited, and that if we would employ it successfully we must have a clear understanding of its limitations and of its narrow field of usefulness.

Too often after satisfying ourselves that the patient's difficulty is due to a failing heart we fall back on digitalis to relieve the situation and neglect the other obvious measures which in many instances may be more effective than digitalis itself.

We should keep in mind the fact that digitalis has no effect whatever in curtailing the incidence of heart disease. The etiologic factors which make for cardiac failure are, as a rule, uninfluenced by the administration of this drug.

The acute infectious diseases such as rheumatic fever which have such a sinister habit of attacking the tissues of the heart are not influenced by this drug.

Wolferth in discussing digitalis states "when dealing with a failing heart, we are not relieved of the responsibility for searching out rigorously the underlying causes of that failure and retracing the course of events so far as possible to the very beginnings of disease. It is not necessary to say that digitalis does not cure faulty habits of life nor infected gall bladders, nor does it materially influence the bad effects of these and like on the heart. Even when—as is too frequently the case—our therapeutic efforts are limited to the symptomatic treatment of heart failure, our attention should be directed first towards securing comfort, rest, satisfactory sleep, adequate functioning of the gastrointestinal tract, and whatever else may be done to ease the burden on the heart."

When we assign digitalis to its proper place in medicine its field of usefulness becomes considerably nar-

rowed. We do not become unreasonable and demand of this drug the impossible. It can never restore elasticity to sclerosed blood vessels, it will not increase the lumen of constricted coronary arteries, it will not replace damaged and fibrosed cardiac muscle, it will not curb the malign activity of bacteria which have lodged in endocardium or myocardium and which there produce inflammatory reaction.

Our ideas regarding the action of digitalis on the heart have been considerably changed in recent years. We have regarded digitalis as a "cardiac tonic," a stimulant to the heart enabling it to perform more work, There is good experimental evidence to show that digitalis decreases the work of the dog's heart and that the actual output of blood is diminished following full therapeutic dosage. Harrison and Leonard showed that the drug caused an average decrease of approximately 25 per cent in the cardiac output per minute of dogs which had been digitalized. They regard the action of digitalis on the heart as similar to that of morphine on the respiration. This conception of digitalis as a cardiac sedative is contrary to current opinion. There is evidence to show that in heart failure the venous pressure is increased and that the heart in diastole fills to a greater extent than it would normally. This results in an increased output of blood at each systole of the ventricles so that the heart is actually required to pump more blood than it would in a normal state. This phenomenon may explain in some measure at least the desire of patients with cardiac failure to be propped up in bed and to insist even on sitting up straight or even leaning forward. In this position the heart puts out less blood at each systole and harm may come to the patient if the recumbent position is insisted upon. Furthermore the cardiac patient will not only assume the upright position but will even feel better, often, if he can get his feet out of bed and allow them to hang over the side. This seems to be the most comfortable position he can assume and patients with cardiac failure may even sleep in this position or when leaning forward on their arms. Digitalis by increasing the tonus of the heart muscle and diminishing the diastolic relaxation tends to break this vicious circle established by the failing circulation.

This evidence would establish several important contraindications to the use of digitalis. If digitalis diminishes the cardiac output its use is contraindicated wherever evidence of diminished cardiac output exists without evidence at the same time of lack of ventricular balance. Such conditions occur in surgical or traumatic shock and after prolonged anesthesia. Digitalis has been widely employed in such cases because of its supposed tonic action on the heart. There is evidence to indicate that the drug may be actually harmful in these conditions.

There is considerable difference of opinion as to the value of digitalis in pneumonia. The evidence is inconclusive at present and there are insufficient data available to definitely answer this question. White in reviewing the records of several hundred patients who had gone through the Boston Hospitals felt that there was

a slightly lessened mortality among patients who had received digitalis. However, his conclusion was that the data were insufficient on which to base a definite recommendation. Many of the cases were given digitalis as a last resort, others received only one or two doses of digitalis, while others received digitalis from the beginning of their pneumonia. This disease offers a particularly fertile field for further observation regarding the effects of digitalis. Leonard and Harrison from their experimental work feel that the drug has been incorrectly used in pneumonia. They believe that digitalis should be given early in the disease and in full therapeutic doses in order to decrease the cardiac output. They believe that digitalis is contraindicated in pneumonia when outstanding evidence of circulatory failure is present. They recommend that digitalis be used to prevent and not to combat circulatory failure in pneumonia.

During the past few months we have used digitalis on alternate cases of pneumonia admitted for hospital treatment. In a series of 20 cases of lobar pneumonia digitalis was given to ten and withheld from ten. These cases were admitted in various stages of pneumonia and the drug was used irrespective of the condition of the patient or the day of the disease but was begun in the alternate cases immediately upon admission. The mortality in the two groups varied very little and favored slightly the cases that did not receive digitalis. This number of patients, however, is insufficient on which to base any conclusion and the series is still being continued in the hope that eventually a sufficiently large number of pneumonia cases will have been accumulated to justify some conclusion regarding this important problem. It would appear, however, that the practice of giving small doses of digitalis in the early stages of pneumonia in order that the heart may be more easily digitalized if the occasion should arise for this action, appears to be unjustified.

Digitalis effect can be secured within six hours even when the drug is given by mouth and there would appear to be no reason for continuing the small dosage during the early days of the disease. No demonstrable effect can be shown from small doses of digitalis.

The question frequently arises as to the value of digitalis in hyperthyroidism. In this condition the state of the heart frequently determines the outcome. While no one would attempt to control the tachycardia and the cardiac damage which results from long continued hyperactivity of the thyroid gland by the use of digitalis, nevertheless this drug is of considerable value in the preoperative treatment of the patient. Digitalis has been frequently maligned because it failed to control the tachycardia and eventual myocardial failure resulting from hyperthyroidism when the thyroid was overlooked as the primary cause of the cardiac failure. However, it is often invaluable in lessening the cardiac output prior to operation and in diminishing the ventricular rate when fibrillation has occurred. When used with this object in view digitalis will not be subject to the

abuse it has received and may be the deciding factor in the patient's recovery following operation.

Digitalis has also been employed as a preoperative measure for a host of different conditions. There appears to be no justification for the routine employment of digitalis in patients with normal hearts before operation. If, however, the patient has evidence of cardiac failure digitalis would be employed in exactly the same fashion as a preoperative measure as it would be in the treatment of cardiac failure without an operation looming up on the horizon.

In past years much confusion existed regarding the efficacy of digitalis in the various types of cardiac arrhythmia. Since the work of Mackenzie much of this confusion has been eliminated. Through the development of the polygraph Mackenzie was able to obtain graphic records of both auricular and ventricular activity and to clearly distinguish and define the various types of cardiac arrhythmia. Up to the time of the polygraph digitalis had been given rather indiscriminately in irregular heart action and the great variability in its result was attributed to differences in the potency of preparations rather than to various types of arrhythmia treated. The effect of digitalis is now well defined and little excuse exists for its abuse in the treatment of cardiac irregularities.

Auricular fibrillation with congestive failure offers perhaps the greatest field of usefulness for digitalis. Its peculiar effect in depressing the auriculo-ventricular conductive system and blocking auricular impulses which bombard the ventricle and cause it to respond at a tremendous rate, results in slowing the ventricular rate and often restores the heart to a fair degree of compensation.

Arrhythmia due to extrasystoles is not in itself an indication for the use of digitalis. Unless there is evidence of associated cardiac failure digitalis as a rule has no effect in lessening extrasystoles.

In the treatment of auricular flutter digitalis is often very effective. Its peculiar action in converting flutter to fibrillation is well recognized and when this phenomenon occurs the drug should be promptly discontinued. If this is done, frequently the rhythm returns to normal.

In paroxysmal tachycardia digitalis is often used and as a rule has little value in cutting short the attack. However, if signs of cardiac failure develop in long continued paroxysms of tachycardia, digitalis can be used to advantage. There is little evidence that digitalis will suppress or avert attacks of paroxysmal tachycardia and its routine use in such conditions is not warranted on the evidence at hand.

In patients who show incomplete heart block digitalis is to be used with extreme caution. Its peculiar property of diminishing conductivity of the auriculoventricular bundle may convert incomplete to complete block with, at times, serious consequences. The advantage of routine electrocardiograms in detecting partial heart block requires no emphasis. If, however, the patient already has complete block and there is evidence of cardiac

failure, digitalis can be used without hesitation.

Distressing attacks of Stokes-Adams syndrome due to temporary occurrence of complete block may sometimes be averted by converting incomplete block to complete block and maintaining it with digitalis.

Before dismissing the cardiac arrhythmias it is well to keep in mind the fact that digitalis is capable of producing every known type of cardiac arrhythmia and in fact may produce types of arrhythmia that can be caused in no other way than by the administration of this drug. Some of the most bizarre electrocardiographic tracings showing every conceivable type of irregularity are produced by the administration of digitalis either in excessive doses or to individuals who are particularly susceptible to this drug. The occurrence of arrhythmia following the administration of digitalis calls for a careful investigation and may be the first indication of the toxic effect of the drug.

When heart failure occurs without any abnormality of rhythm digitalis is still effective if given in adequate doses. While it may be particularly effective during the first or second attack of cardiac failure, not infrequently, with subsequent attacks its value is less and less marked. This is the natural phenomenon to expect and should not lead to the abuse of the drug. As the disease process becomes further advanced, as the coronary circulation becomes increasingly impaired, as the myocardial muscle becomes replaced by fibrous tissue, digitalis becomes less and less effective in maintaining an efficient circulation and eventually is entirely ineffective.

There is no more distressing picture than that of the patient slowly and painfully dying of congestive heart failure. The scene is familiar to all of us—the patient upright in bed, gasping for breath, using all the accessory muscles of respiration in order to compensate for a failing oxygen supply, cyanotic, with distended limbs and abdomen and frequently hydrothorax, unable to get a minute's rest or peace and looking forward with relief to the moment when his suffering will be ended by death. There comes a time in the final stages of every cardiac patient when digitalis fails to sustain the circulation. These patients may take days or even weeks to die. When this stage arrives morphine offers the patient the greatest solace, and digitalis even if pushed to the point of beginning toxic symptoms eventually loses its potency and must acknowledge defeat.

We would do well to look forward and bear in mind this distressing end picture which faces our cardiac patients. While many of them succumb to intercurrent infections or are removed from the picture by contact with a swiftly moving automobile, a fair percentage reach this end stage. This fact should stimulate us to safeguard the heart by every possible means in the early stages of heart failure knowing full well that eventually digitalis will no longer perform this important task for us. The elimination of foci of infection, the regulation of the patient's hygiene, the careful supervision of the dietary, the

regulation of the hours of work, sleep and rest, are measures which are equally if not more important than the adequate administration of digitalis.

In valvular heart disease digitalis is often abused. Not infrequently we see following the diagnosis of a valvular lesion, a prescription for some form of digitalis. Valvular heart disease itself is not an indication for the use of this drug. When heart failure occurs and accompanies a valvular defect then digitalis may be used with benefit.

In patients with valvular heart disease the myocardium and the coronary arteries frequently participate in the damage. It is not the state of the valves so much as the state of the myocardium which determines whether or not digitalis is indicated.

The practice of prescribing digitalis for patients who show a heart murmur and no evidence of cardiac failure cannot be too strongly condemned. It is a potent source of cardiac neurosis.

In that symptom complex, angina pectoris, the question frequently arises as to the advisability of employing digitalis. There remains much for us to learn regarding this peculiar syndrome. That it indicates grave cardiac damage no one questions. We frequently find at the postmortem marked sclerosis of the coronary arteries and lesions which would suggest that the patient had suffered from angina pectoris and yet after a careful perusal of the history learn that the patient at no time suffered from this symptom. Why it should occur in one individual and not in another with similar pathological lesions remains unexplained. The pathologist cannot diagnose this condition either from the gross pathological anatomy or with the microscope. Digitalis is as a rule ineffective in combating the attacks and its employment in this condition is generally without avail.

Since Eggleston has placed sanction on larger doses of digitalis untoward symptoms have been more common. If we would keep in mind Eggleston's warning regarding the use of massive doses this effect would be less frequent. In commenting on this dosage Eggleston remarks "the use of large doses is not a safe procedure unless the patient can be under nearly constant observation and unless the effects of treatment can be graphically recorded at frequent intervals." It is not always easy to determine when the maximum or safe dose has been reached. If we obtain the desired result the dosage is adequate and further use of the drug is contraindicated. Frequently however, before we obtain the desired result one or more symptoms of a toxic nature develop to warn us that we have reached the limit of safety as far as dosage is concerned.

Cushny has aptly compared the administration of digitalis by massive dosage to a simple chemical titration in the laboratory. Where the strength of the reagent is known, it is safe to run in from the burette a relatively large quantity of salt, and then complete the reaction with a few drops as the end point is reached.

Bastedo has laid down the following excellent rules as to when to stop digitalis.

1. Digitalization as shown by the electrocardiograph.

2. When the desired effect is accomplished, as by the disappearance of dropsy or enlargement of the liver, or by the slowing and steadying of the pulse in auricular fibrillation.

3. Nausea and vomiting ensues.

4. If the patient complains of headache, anorexia and dizziness or lightheadedness.

5. The cardiac rate goes below 60.

6. The rate slows suddenly.

7. Coupled rhythm appears.

8. Premature beats occur.

9. A regular rhythm becomes irregular or intermittent.

10. Sinus arrhythmia or phasic arrhythmia occurs.

Carr, from the Cook County Hospital, Chicago, calls attention to digitalis delirium which he has observed and which he feels is frequently overlooked as one of the toxic manifestations of the drug.

Quite recently our attention has been called to eye symptoms produced by digitalis. Sprague, White and Kellogg state "these disturbances are very infrequently recognized in this country, in the French and German literature, however, visual disorders from digitalis have been well described." Even Withering himself called attention to this phenomenon and states that occasionally there is noted obscured vision, objects appearing yellow or green. Occasionally symptoms of toxic amblyopia with dimness of vision, flickering and flashing scotomas, and marked disturbance of color vision occur. It is believed that these visual disorders from the use of digitalis are more common than is generally supposed.

We have attempted to indicate some of the ways in which digitalis may be abused. A remarkable drug, a fascinating remedy to study and when properly employed a drug whose place cannot be filled at present by any other known remedy. A drug, the study of which has employed the time and energy of some of the most brilliant minds in medicine.

Withering, Mackenzie, Cushny, Price, Hatcher, Eggleston, Robinson are some of the names which will probably always be associated with the history of digitalis.

These accumulated data regarding digitalis are a particularly rich heritage which fall to the student of medicine today. It behooves him therefore to employ this heritage properly, to be well versed and familiar with all phases of therapeutic activity of the drug. In his zeal, however, he should ever keep in mind the well defined limits of its field of usefulness. A powerful drug, potent to do harm when used indiscriminately, the margin between safety and danger is a particularly narrow one. Its ability to cause serious damage and even death should never be lost sight of. An agent requiring delicate and skillful handling, its administration should never be left to untrained hands.

Diabetic Therapy, With Special Reference to the Newer Remedies*

By Arthur A. Herold, M.D., F.A.C.P., *Shreveport, Louisiana*

THE literature of today is teeming with articles on diabetes mellitus and especially with its therapy; there is probably no subject which has engaged the thoughts of a higher class of medical minds than this one. Such leaders as Allen, Joslin, Wilder and Woodyatt in this country; Banting, MacLeod and Campbell in Canada; and von Noorden, Minkowski, Cammidge and others abroad demonstrate, by their unceasing interest, not only that the riddle of diabetes is fascinating, but that it will be solved! By this, I mean that, whereas, by various methods of therapy, which we shall detail in this paper, the disease may usually be controlled, still we have not yet reached the point where we might put the letters "Q.E.D." after the diabetic problem!

The scope of this paper does not permit of a consideration of the etiological factors in diabetes, except insofar as they pertain to the subject of therapy; I trust that you will bear with me, therefore, while I briefly refer to historical data, leading up to modern treatment. The classical experiments of Claude Bernard, during which he demonstrated the famous "piqûire" or puncture of the tip of the calamus scriptorius in the fourth ventricle, causing a glycosuria, with depletion of liver-stored glycogen, may be designated as the starting point of thinkers, searching for rational diabetic therapy. As far back as 1682, Conrad Brunner attempted total pancreatectomy on dogs, in trying to solve the etiological problem; it was not until 1889—or 207 years later—that Von Mering and Minkowski successfully carried out this experiment and gave to the world the information that severe and fatal diabetes is caused thereby. Although Paul Langerhans first described the islands in the pancreas, bearing his name, in 1869, it was not until 1901 that Opie demonstrated that these are the elements involved in pancreatic diabetes.

While investigations by the abovenamed and numerous others were being conducted, both in etiological studies and attempts at specific therapy, what was being done by the army of practical clinicians in treating the increasing number of cases that were presenting themselves? Up to this century, very little progress was made in therapy; it was realized, of course, that carbohydrate metabolism is dis-

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turbed and the sole aim seemed to be to minimize the intake of that food element—too often with quick disastrous results. About 1900, under the influence of the German schools, especially Naunyn and his coworkers at Strasburg, followed by von Noorden and his associates at Frankfort, the dietetic treatment was handled more scientifically, with the results that undernutrition and acidosis were prevented—at least, for longer time—and the average life of the diabetic prolonged; we understand better today than was understood then why von Noorden often got good results with his oatmeal "cures." Then, about 1914, Allen advanced the method of prolonged fasting and undernutrition, which was first received with misgivings by many who had seen fatal starvation-acidosis; but, it was not long before the skeptics had to admit that, if properly carried out, as outlined by Dr. Allen, it accomplished more for the severe cases than anything yet proposed; Joslin's statistics on this are thoroughly convincing. An Italian, named Guelpa, also carried out fasting, along slightly different lines, with improved results in his cases.

Diabetic therapy was revolutionized when, on February 22, 1922, Banting and Best, with their associates, first gave out reports of the successful use of their product in human beings, seven cases being reported. Their work followed the researches of Minkowski and the others, above referred to; they had found what workers had been anxiously looking for ever since the announcements of Von Mering, Minkowski and Opie. In some quarters, the announcement was received with skepticism, while the overenthusiastic expected too much; it was some time before the discovery could be properly evaluated and then it was realized that, with "insulin here" (to use Joslin's expression), the proper regulation of the diet became of more importance than ever—this, I might add, being to the thorough disgust of many diabetics, who soon formed the idea that, when taking insulin, they could be turned loose in the confectionery. Although some of the best clinicians of today do not agree with him in toto, Woodyatt's ketogenic-antiketogenic formula of $F = 2 \times C + P/2$, with total calories depending upon weight, physical activities, etc., holds good. Opinions differ as to relative amounts of protein and fats, most authorities figuring the protein at 1 gram or less per kilo of body weight, Newburgh and Marsh, for example, believing in a higher fat and lower protein than Allen and his followers; certain it is that most diabetics take proteins better than fats, but the glucose-equivalent of the former is so much more than of fats, that this must be reckoned with; on the other hand, under-nourished diabetics may be built up rapidly with higher fats, in order to increase the total calories, provided the carbohydrate and insulin be also kept comparatively high, in order to obviate the danger of ketosis. In this respect, it would not be amiss to mention the fat-substitute, with the odd molecule, which, it has been shown, is incapable of being converted into acetone bodies; this preparation was worked out by the late Dr. Max

Kahn of New York and named "Intarvin" and, although I have had no personal experience with it, I can readily see where it would prove of great value in arranging the diet of those severe diabetics who are prone to develop this dreaded complication.

As to the administration of insulin, I feel that it is pretty well agreed today that the majority of cases can be controlled by giving it twice daily, before breakfast and before the evening meal, the dose varying according to the diet (total carbohydrate-equivalent and, especially, total calories); severe cases require, sometimes, more frequent dosage and, of course, surgical complications and acute intercurrent diseases necessitate increases, but, what I mean to bring out is that, considering the indications, comfort and mental attitude of any case, two doses per day is generally the happiest solution. It is, usually, preferable to give a larger dose in the morning than in the afternoon, for obvious reasons; from time to time, the dosage has to be varied, as we are constantly, when trying to keep the patient's blood sugar around normal—especially in children—between the Scylla of hyperglycemia with its complications and the Charybdis of hypoglycemic reactions. Although the literature contains reports of insulin-resisting patients, I have been fortunate enough not to encounter any of this genus and am always suspicious, when reading these accounts, that there may be other factors, escaping the watchful eye of physician or nurse, as illustrated by the following case, which came under my observation three years ago: A boy of 12, patient in a charity hospital, maintained glycosuria and hyperglycemia, in spite of careful dieting and gradually increasing insulin dosage. One day the picture suddenly changed and he was found in profound coma, cold and clammy; his urine was sugar-free and blood sugar was .045; after his revival with intravenous glucose, it was learned that his friends had been smuggling fruit and candy to him until that day, when, through the influence of the boy's relatives, the supply had been suddenly cut off, without apprising the resident physician of the facts.

Other factors, too numerous to mention here might enter into these cases. However, be that as it may, although we have an invaluable therapeutic aid in this preparation, we cannot call it a "cure" in the true sense of the word; we may tide our patients over complications, we may improve the tolerance of the milder cases and we may help all diabetics with it, for, as Joslin says, there must be, in addition to the sugar-consuming properties, an indefinite something in insulin, which contributes to the well-being of the diabetic; for this reason, he feels that a small dose, once daily, is helpful even to the milder cases.

In looking for a "cure" and in trying to obviate the hypodermics, so repugnant to some, we hope to find a suitable oral remedy. Dating back to pre-insulin days, various pharmaceutical and biological firms have laid claims to remedies that either palliate or cure the diabetics; some of these claims, I might state, to use an expression which I heard from Dr. Cushing, are "simply harrowing"!

It is useless to enumerate the yeast products and the pancreatic derivatives which have been, and still are, offered to us as a panacea for this perplexing disease. However, the most hopeful substitutes for insulin have come from Germany and the Nobel prize commission, which, a few years ago, awarded the honor in medicine to the discoverers of insulin, has seen fit to bestow the same, in 1927, upon Prof. Frank of Breslau for producing one of these preparations, known as "Synthalin." Others which I have investigated and packages of which I am showing you today, besides Synthalin, are Fermocyl, Reglykol, Glukhorment. In a personal communication, Prof. von Noorden states that the first two are not highly considered in Germany and that they are handled over the counter by the pharmacists, whereas Synthalin and Glukhorment are prescribed. Fermocyl is said to be a yeast product, whereas the published formula of Reglykol states that it contains no guanidin or derivative.

My personal experience with these preparations is limited to three cases, in which I have used synthalin, brief details of which follow:—

Case I. A. H., aged 6; diabetes of over 4 years duration, during most of which time he has been on insulin therapy. Tablet of .010 gms. synthalin given for two nights in succession and then omitted every third night. Patient would get some manifestations of hypoglycemia about 14 hours after administration of drug; this stopped after reduction of morning dose of insulin. No gastrointestinal disturbances.

Case II. C. S., aged 37; diabetes of 9 years duration; has used insulin somewhat irregularly, for past 4 years. Tablet of .025 gms. synthalin taken twice daily for two days and omitted on third. Was able to reduce insulin materially, but finally quit the synthalin, as he said that the reducing of blood sugar made him weak and he did not know how to control it, as he did with insulin dosage. No gastrointestinal symptoms.

Case III. S. C., aged 6; diabetes of 6 months duration, during most of which time she has been on insulin. Took .010 gms. synthalin every night for three nights, then skipping one night; results same as in first case and no gastrointestinal symptoms.

Synthalin is a synthetic compound, de - camethylene - diguanidine, introduced by Frank and associates, from Minkowski's clinic in Breslau in December, 1926; practically all the reports give it credit for reducing blood sugar, but it is generally claimed that the gastrointestinal irritation produced by therapeutic doses prohibits its general use; the firm of Kahlbaum, which placed it on the market, claim that it acts like insulin, by supplying something to the system, which produces glycolysis. An interesting discussion has arisen in Germany on this point, one observer contending that its effects are liable to be harmful, in that its results are obtained only by overstimulating the already weak internal-secreting islands of Langerhans; this contention, however, is vigorously denied by the sponsors of the drug. I wish to call attention to the fact that, in my limited experience, no irritation of digestive tract was observed, but I have discontinued use of the preparation, partly on account of the warnings and partly because of difficulty in obtaining it in this country. A few months ago, Eli Lilly & Co., who, it will be remembered, were the first in this country to produce a commercial insulin, under license from the Toronto group, undertook an investigation of synthalin, with the idea

that, if reports justified, they would handle it, commercially, in the U. S. Under date of February 6, they inform me that they are still investigating this product, as well as a later one, neo-synthalin, but that they are not yet sufficiently satisfied to justify making definite statements; further, that Prof. Frank recently visited their laboratories and agreed with them in their conservative attitude; they state, also, that neo-synthalin appears to be less liable to produce gastrointestinal irritation than its precursor. Dr. A. I. Ringer of New York who has been investigating these preparations, writes me, under date of February 20, that, although he has seen decided lowering of blood sugar, with disappearance of glycosuria, still he hesitates to recommend synthalin, owing to its frequent gastric irritation; as to neo-synthalin, it has been inert in his hands.

Now, concerning Glukhorment: When a relative of mine was in Karlsbad, last year, he made inquiries for me concerning synthalin; he was told that it was feared, on account of the digestive disturbances, but that a newer and better preparation, in use there, was Glukhorment, it being endorsed by Prof. von Noorden. I have never tried it, personally, but, some time later, I read that von Noorden had withdrawn his endorsement therefrom; anxious to know the truth, at least before using it on a patient, I wrote to him and he was kind enough to reply freely, part of which I quote below:—

"Glukhorment is an undoubtedly effective and useful preparation and decidedly more agreeable than Synthalin, even though it may be better sometimes to pause one or two days, after a 3 to 4 days' use, on account of the stomach. . . . . According to the present state of investigation, there is no doubt but that there is present in Glukhorment, in a considerable quantity, a chemical body which is similar to and possibly even identical with Synthalin. As I already said in my paper of November 8, 1927, the chemist of the Horment Company still absolutely denies that Synthalin is added while, on the other hand, the Schering factory in Berlin, manufacturers of Synthalin, declare the opposite. As it is impossible to decide the question, definitely, by chemical analysis, the two interested powers have, with my consent and, partly on my suggestion, sued each other in the courts. From the resulting evidence and testimonies, the actual truth will be finally determined. . . . . In my clinic, we have ceased long ago, even before the advent of Glukhorment, to administer Synthalin, as the concomitant disturbances were too frequent and intensive."

Prof. von Noorden also referred me to an article by Prof. Dale of London, published in the British Medical Journal of December 3, 1927, in which he shows proof that, in spite of von Noorden's statement to the contrary, either synthalin or a similar guanidine derivative is present in Glukhorment; when Prof. Dale apprised von Noorden of his findings, he (von Noorden) had just received similar disconcerting evidence from another quarter; this, then, is what gave the impression that he had renounced Glukhorment—he did not renounce it in toto, but he asked the medical world to suspend judgement, on the strength of his

statement that it contains no synthalin or other guanidine derivative until the truth may be brought to light, as outlined in his letter.

All of the above strikes us as a tribute to the effectiveness of synthalin! Now, Dr. Ringer, who, as above stated, has noted the decided lowering of blood sugar with synthalin, informs me that he has noted no such effiect, whatsoever, from glukhorment.

A paper of this kind would be incomplete were it not to call attention to the various products of the vegetable kingdom that have been used with more or less success and, especially, refer to the interesting and hopeful work of Allen with myrtillin.

Natives in various rural districts have empiric knowledge of the action of decoctions or other preparations of domestic plants in lessening polyuria, which is so often (might we say, usually?) glycosuria. In Prof. von Noorden's lectures on diabetes, delivered in this country, in 1905, he stated: "About 15 years ago, Prof. Binz and Dr. Graser discovered that the fruit of the East Indian plant, Syzygium jambulanum, possesses the property of strongly reducing phloridzin diabetes. As both the dried fruits and their extracts have proved themselves to be quite harmless even in large quantities, it is not surprising that new experiments are always being made to see whether the glycosuria of true diabetes cannot be alleviated or cured by it. . . . . I have,, myself, employed and studied the effect of jambul preparations on cases of severe and slight diabetes; the results showed that, in some cases, a marked effect on the glycosuria was, without doubt, actually obtained."

Not long ago, Root and his associates in Joslin's clinic called attention, in an article in the Archives of Internal Medicine, to the beneficial effect of "Jerusalem artichokes" in many cases; they mentioned the fact that the starch in this form not only does not raise the blood sugar, but that, often, while getting nourishment, the diabetic has been known to acquire an increased tolerance while using this root-article of the potato family, properly prepared.

Allen tells us that, in certain districts in Hungary, the peasants have known for years that a decoction or tea of certain blueberry leaves helps the polyuric; on this information, conveyed to him by his chemist, he has experimented with the preparation which he has named "Myrtillin." While he makes no extravagant claims for it, he states that, given an adult diabetic whose blood sugar has been brought to normal, with diet and insulin, myrtillin will, as a rule, keep him in good condition, which is certainly encouraging, to say the least.

To sum up, then, we feel that the outlook is bright for more help for the large army of diabetics; we believe that, although, for the present, our main reliance shall continue to be insulin and proper diet, the many investigators working on this problem will soon be rewarded; especially, do we feel that Frank and his associates have blazed a trail and that something on the order of synthalin will soon be found, which will prove a boon to these unfortunates and will replace insulin, as a routine, but not of course in coma, surgical complications and in very severe acute cases.

A Consideration of Natural and Acquired Body Resistance to Neoplasia*

By J. L. Goforth, M.D., *Dallas, Texas*

DESPITE extensive investigation and experimentation in practically every possible line of study in the field of neoplasia, so little has been learned that the cancer situation still confronts the medical profession as a baffling and largely unsolved problem. It has not been demonstrated that the body tissues can develop immunity to neoplasia, either naturally or artificially, and until the causes and more of the nature of the disease are determined, immunology probably will be of little aid in combating it. The body tissues, however, do build a type of resistance of greater or lesser degree, to neoplasia in the majority of instances. The activities of this defense mechanism are recognizable and demonstrable microscopically chiefly, and are evaluated in the analysis of the relationship that exists between host and neoplasm—a procedure which is essentially a histopathologic study. The age of the patient, the duration of signs and symptoms, the location, gross form, and extent of the tumor are all important indices to prognosis from the clinical point of view, but are not considered in this study.

Many diseases are associated with increased or diminished rate of multiplication of some of the specific component cells of the body. Whatever the etiology of cancer may prove to be, whether a parasitic, a physiologicochemical change in certain groups of cells, a cellular response to continued chronic infection and irritation, a spontaneous growth-impulse occurring in cells which are misplaced anatomically, or an hereditary phenomenon, it seems certain that some stimulus, as yet unknown, possesses the definite capacity to cause local multiplication of cells that have apparently functioned as normal cells prior to the action of the stimulus. This lawless proliferation of cells is neoplasia, and the reactions of the body tissues to this misdirected and anarchic growth-impulse constitute the host's natural defense mechanism.

Strauss (1), in an interesting study based on the thought that the observance of the spontaneous disappearance of clinically and histologically malignant tumors might throw light on the working of the natural protective mechanism of the body tissues to neoplasia, this in turn leading to methods

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of increasing body resistance which would be of therapeutic value, found only 53 cases in the literature which he accepted as spontaneously disappearing malignant neoplasms. This would tend to show that natural resistance unaided is able to overcome neoplasia in small measure only. It is my purpose to try to show that in dealing with neoplastic disease, the proper procedure will have not only a destructive effect on the growth locally, but also will augment and strengthen the working of this natural defense mechanism.

Microscopic study of tumor tissue not only permits of the classification of the neoplasm, but establishes its structural form and cell-type, and gives valuable information regarding the reaction of the body tissues to the invading tumor. Cancer cells tend to reproduce the cell-type and structures from which they are derived, and the rate of growth of a given tumor determines in a large measure the degree of perfection of this tendency. Just as the normal growth impulse of tissues tends to wane as the body ages, in neoplasia, as a general rule, the older the patient is, the slower does the tumor grow, the later does it metastasize, and the more differentiated is its cell-type likely to be.

Cell-type determination is particularly important in that the information thus afforded regarding the degree of maturity of the predominating cells composing the neoplasm is of guiding value in the choice of treatment procedure. Cells of immature or undifferentiated type, exert so much of their energy in reproduction that they do not have time to approach the mature form which their prototypes normally assume. They grow more rapidly, and by reason of their embryonal nature, are more vulnerable to certain destructive physical agents, such as radium and the roentgen-ray, than those of greater differentiation, or more adult type. The seeming handicap of rapid rate of growth common to those neoplasms composed of unripe cells often may be partly offset because of the "radio-sensitiveness" of the tumor cells. The degree of differentiation of neoplastic cells is so readily estimated that it has become a routine procedure in several cancer clinics. A frozen section preparation of a small sample specimen of tumor tissue is sufficient for the determination in the hands of a trained tissue pathologist. It is my feeling that each case of neoplastic disease should be treated as an individual problem, and the general plan of attack should include biopsy study of the tumor tissue as early as possible in order that cell-type and differentiation determination may serve as a guide in the choice of the therapeutic agent to be employed. Such procedure is both rational and scientific in the present state of our knowledge of cancer.

The activities of the several natural factors of body tissue defense vary considerably in the different types of neoplastic disease. Fibroplastic tissue proliferation occurs spontaneously in greater or less degree about the advancing edge of many neoplasms. This fibrous tissue often gradually condenses, becomes very tough and firm, and may undergo hyalinization. The resulting scirrhous mass may be

thought of as an ever-constricting network of local body defense enclosing and attempting to obstruct, limit and choke the progress of the new growth. It is a well established fact that irradiation promotes fibroblastic tissue proliferation locally. In those instances where the use of radium or roentgen-ray, or any other fibrous tissue stimulator, is indicated, the treatment may be regarded as actually augmenting body resistance in addition to its primary function of destroying the neoplasm.

The spleen has been an interesting subject of study and experimentation because of its well known antagonism to neoplasia. In a series of 6500 necropsies, Krumbhaar (2) found only 40 splenic tumors; 21 of these were secondary carcinomatous growths, and 12 were sarcomatous deposits. It is noteworthy, too, that lymph nodes receiving drainage from tumor-bearing areas frequently exhibit a remarkable proliferation of sinus endothelium. Jaffé (3) states that metastases are less frequently found in nodes showing endothelial hyperplasia than in those where the endothelium has not reacted. Such a tissue reaction occurring in the major reticulo-endothelial centers finds a possible explanation in the anticancerous action of the reticulo-endothelial cells themselves, and when it is recalled that wandering endothelial cells or clasmatocytes of phagocytic capacity are frequently demonstrable about the advancing borders of malignant growths, the function of the reticulo-endothelial system as an important agent in the defense of body tissues against neoplasia seems quite plausible. Jaffé (3) in a recent interesting study of the rôle of the reticulo-endothelial system in pathologic conditions found that the cells of this system could be influenced therapeutically. A reduction of the endotheliocytes follows splenectomy, and roentgen-ray applications in small dosages, the injection of non-specific proteins, and the intravenous injection of certain dyes and colloids all tend to stimulate these cells to multiplication and activity. As more is learned regarding the actions and behavior of this widespread and wandering body tissue, the possibility of mobilizing and employing it in the attack on cancer through the use of stimulative therapy is strongly suggested.

The local accumulation of large numbers of lymphocytes and plasma cells in addition to the endotheliocytes above referred to, constitutes a defense measure frequently employed by the host in combating chronic progressive infections of many types. In neoplasia the gathering of these cells throughout the tumor and fibroblastic tissues surrounding the growth is often observed, particularly when there is associated with the neoplasm a chronic, secondary infection. In studying the responses and reactions of the tissues of the body protective mechanism to various methods of tumor therapy by means of repeated biopsy examinations at different periods of the tumor's course, I have often noticed a progressive increase of this mononuclear infiltration locally as the neoplasm yields to treatment. It has not been definitely determined whether these cells can be influenced therapeutically, but I believe they play some rather important rôle in inhibiting the

extension of both the infection and neoplasm.

In another study (4), the eosinophil was considered as having protective properties against neoplasia. Relatively little is known about the eosinophil, or its function. It has long been known that the eosinophils increase in number in intestinal parasite infestations, bronchial asthma, anaphylactic and allergic reactions, certain chronic diseases of the skin, and certain chronic inflammatory processes such as pleural effusions, chronic active appendicitis, and chronic pelvic infections. It is also usual to find an eosinophilic infiltration of the tissues which are the seats of these conditions. In myelogenous leukemia, which may be considered a form of neoplasia, striking eosinophilia is the rule. In the study of squamous cancers of all locations, and the adenocarcinomas of the gastrointestinal tract, I have been impressed with the observation that in those instances where local eosinophilia has obtained, the patient has exhibited a greater resistance to the neoplasm, has responded better to treatment, and has lived longer than when eosinophils were not present. In a recent study of 417 radiologically treated cases of squamous carcinoma of the cervix, Schoch (5) found that in the 40 cases with local eosinophilia the proportion of five years cures was 45%, while in the three hundred and sixty-seven cases without eosinophilia, it was only 10%. In a recent analysis of the behavior of the several body defense tissues in a group of epidermoid cancers of the cervix which I have followed, especial attention was given the eosinophil. This study indicates (1) that the eosinophils in the circulating blood, as determined by the differential count, increase in percentage as the eosinophilic infiltration of the tissues about the neoplasm becomes more prominent; (2) that the greater the number of eosinophils both locally and in the blood stream, the more favorable is the prognosis, and (3) that irradiation tends to promote eosinophilic activity and multiplication. I regard the presence of the eosinophil as a good omen in malignant disease, and consider it a valuable index to prognosis in addition to its being an important defense agent against neoplasia.

In the light of these considerations, the logical and rational treatment of cancer resolves itself into a plan of attack having a double objective, namely, (1) the eradication of the disease locally, and (2) the augmentation of the patient's natural resistance to further or recurrent neoplastic growth. This, I feel, may be best accomplished by routine thorough study of each neoplasm both grossly and microscopically, followed by the application of the form of treatment best suited to the individual neoplasm. It has been demonstrated that certain tumors will respond well to one method of treatment, and poorly to another. The information obtained through the procedures and considerations above outlined enable one to forecast relatively accurately the response that may be expected of a given neoplasm to the various methods of therapy, and, in my experience, has proved a very helpful guide both in the selection of the therapeutic agent of greatest prob-

able efficiency, and in the method of its application.

Without attempting to evaluate in detail the relative merits of the several standard methods of neoplasiotherapy at present in use, I wish to point out that radical surgical procedure has apparently very nearly reached its high point of efficiency in combating neoplastic disease in several locations that are favorite sites for tumor growth. There is a tendency to determine the operability of a neoplasm from the gross or clinical point of view. When it is recalled that infiltrative neoplasms often extend far beyond the area that forms the gross tumor mass, it is evident that many so-called operable growths are in reality quite inoperable. Attempted surgical extirpation of such tumors fails not only in the eradication of the disease but actually interferes with and curtails the activities of the natural body defense mechanism to neoplasia. A certain group of neoplasms belong properly to the field of surgery, and I feel that surgical activity should be limited to these.

Radium and roentgen-ray therapy, properly and scientifically employed, have proved very efficacious in both arresting and eradicating certain types of neoplastic diseases. As pioneer agents, relatively speaking, they promise much in the further development and extension of their usefulness in the attack on neoplasia because of their destructive action on the large group of radio-sensitive tumors, and their stimulative effect on several of the body defense tissues.

The combined employment of surgical methods and radio-therapy, with, in appropriate cases, the additional aid of adjuncts such as the cautery and electro- and chemo-therapy, offers an approach to a third large group of neoplasms that yield neither to operative procedure nor irradiation alone. The use of the cautery in destroying much of the tumor largely for facilitating the more accurate and efficient placing of radium has given excellent results in many instances. In many of the so-called "hopeless cases" of cancer, combination therapy, as above indicated, while not curative, often retards the progress of the disease, thus affording additional time for the working of the body defense agents, and offers the patient temporary relief from the ravages of the disease.

As the proper information regarding cancer is disseminated among the laity, the various types of malignant disease will be seen in earlier stages, and differential diagnosis correspondingly will become more difficult. In order that each patient with a tumor complaint may be given the obvious advantage of the indicated treatment at the earliest possible moment, it is apparent that all anticancerous forces must be called into united action. The cancer problem does not belong exclusively to any one of the major divisions of medicine; it is a problem facing the entire medical profession, and only by combining the tumor knowledge, the various aids in diagnosis, and the different methods of treatment of the fields of surgery, internal medicine, radiology, and pathology can any headway in the conquering of neoplasia be hoped for.

Summary

1. An analysis of the relationship that exists between host and neoplasm

is presented. The reactions of certain body tissues to neoplastic growth constitute the host's natural resistance to neoplasia.

2. The histologic type of tumor cells, particularly the degree of differentiation of the predominating cells of a neoplasm, is a reliable criterion upon which to base prognosis from the pathologic point of view, and should serve as a guide in the choice of the therapeutic agent to be employed. Biopsy study should be an early routine procedure in the plan of attack on each malignant neoplasm whenever possible.

3. The activities and behavior of the several tissues playing rôles in the body protective mechanism against neoplasia, are evaluated as follows:—

(a) The proliferation of fibroblastic tissue about the advancing edge of many neoplasms tends to limit and obstruct the progress of the growth. Radiotherapy stimulates the activity of this defense factor.

(b) The antagonism of the reticulo-endothelial system to neoplasia is discussed. The possibility of influencing endotheliocytes therapeutically in the attack on neoplasia is suggested.

(c) Lymphocyte and plasma cell infiltration of and about tumor tissue tends to inhibit the extension of the neoplasm and the secondary infection that is often present.

(d) The eosinophil is a valuable index to prognosis in addition to its being an important defense agent against neoplasia.

4. The rational treatment of neoplastic disease should have a double objective: (1) the eradication of the tumor locally, and (2) the augmentation of the host's natural resistance to further or recurrent neoplastic growth. Each case of malignant disease should be considered as an individual problem, and the form of treatment best suited to the growth as determined by the several reliable guide factors above mentioned, should be applied.

5. The cancer problem faces the entire medical profession and calls for united and cooperative endeavor from each of its special divisions.

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The Influence of the Tropics on Rickets*

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About the year 1650 Glisson, the distinguished English physician and physicist, as the result of an extended study concerning what was believed to be a new disease, published a monograph on rickets. Since the appearance of his notable paper down to scarcely more than a decade ago, progress in our knowledge of this common disease of childhood has been slow and of little clinical value. During the past ten years, however, many material and valuable discoveries have been made, due in great part to the able investigations of Mellanby, Huldschinsky, Howland, Schmorl, Findlay, McCollum, and that tireless and fruitful worker, Hess, of New York. In spite of the many advances made in our knowledge of rickets in recent years, much remains to be learned, especially as to details of etiology.

What I shall have to say today is based upon a review of the recent literature, a study of 100 white and 100 negro children in Panama in 1925 and 1926, and a few observations made in New Mexico and the Philippine Islands fifteen or more years ago.

It is believed that a brief summary of the more important discoveries in respect to and current views on rickets will facilitate the orderly and logical consideration of my theme.

It is generally recognized that rickets is a constitutional disease of infancy manifested by disorders of nutrition and metabolism. The most obvious disturbance is an inability of the organism to deposit or fix calcium phosphate in the growing bones. As a result, the bones lose calcium, become soft and in advanced cases bow or bend. Long bones grow at the epiphyseal junction. In rickets, marked and characteristic changes occur at this line, to wit: marked proliferation of the osteoid cells, failure to take up or retain calcium, increase and ingrowth of capillaries from the diaphysis to the epiphysis and thickening of the periosteum due to a deposit of cartilaginous and osteoid tissues about the cortex. These pathological changes give rise to enlargement and softening of the epiphyses, especially those at the wrists, ankles and costochondral junctions. Normally the epiphyseal line as depicted in the X-ray film is straight and well defined; in rickets, due to the afore mentioned changes, it becomes ragged and ill defined. The flat bones of the head and pelvis may lose so much calcium as to crackle and crumple with result-

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ing deformity of the cranium and pelvis.

Many other equally important, however less obvious, changes take place. The muscles become soft and flabby, the nervous system irritable, and the lymph tissues proliferate. The blood calcium normally 10 to 11 mg. to 100 c.c. of volume may be normal or reduced in amount. The inorganic phosphorus content—normally 5 mg. per 100 c.c. of serum—is quite constantly and materially reduced. From the diagnostic standpoint the phosphorus level has assumed importance. In rickets manifested by tetany the calcium is low and alkalosis often present. When the calcium is normal the tendency is toward acidosis. Howland states that rickets does not occur unless the product of the calcium and phosphorus content in mg. per 100 c.c. of serum falls below 40 to 30.

Why the bones are unable to fix calcium, in spite of the fact that the blood level may be normal, is one of the many unsolved problems in rickets. Some believe the absorption of calcium from the intestines is just sufficient to maintain the normal blood level, but is inadequate to permit utilization by the bones. Others that absorption is normal but excretion excessive. And finally, still others that neither absorption nor excretion are faulty but that the bone cells are unable to fix and retain calcium due to an insufficient supply of the antirachitic factor often termed vitamin D.

McCollum and his co-workers found that in animals the ratio between calcium and phosphorus in the diet is very important and may be of greater significance than the absolute amounts present. Present day evidence is to the effect that an infant's diet is rarely or ever so deficient in minerals as to be an important factor in the production of rickets.

Mellanby discovered in 1918 that many animal fats contained a substance which would prevent rickets. He originally regarded this as vitamin A (fat soluble.) McCollum ascertained in 1922 that the active body was not vitamin A and designated it the antirachitic factor. In the literature of today it is frequently termed vitamin D; however, many investigators object to this appellation on the ground that its identity is as yet undetermined. It is the principle so abundant in cod liver oil and so potent in the prevention and cure of rickets.

In 1919 Huldschinsky made the epoch-making observation that ultraviolet rays generated by the mercury quartz lamp would cure rickets. Two years later, A. F. Hess discovered that the ultra violet rays of the solar spectrum were likewise efficient in the prevention and treatment of rickets.

It is now generally conceded that three factors play a rôle in the etiology of rickets:

1. Ultra-violet rays
2. The antirachitic factor commonly called vitamin D.
3. Unbalanced diets

Most authorities regard an insufficiency in quantity or quality of ultraviolet rays as by far the most important factor in the production of rickets in children. A deficiency or disproportion in the ratio of calcium and phosphorus is rarely a cause of rickets except in experiments on animals.

It is generally accepted that rickets is uncommon in the tropics and mountainous regions where sunshine is plentiful and an abundance of solar ultraviolet rays present. Why ultraviolet rays are so abundant under the conditions mentioned will be explained later on.

It has been common knowledge for years that rickets is also rare in the Arctic Zone and certain other localities where the amount of sunshine is small and the humidity high, as in the Baltic Basin, the Hebrides, and Western Ireland. In such regions it is obvious that sunshine plays a small part in the prevention of rickets. The inhabitants in these regions subsist largely on fish, animal fats and livers, even the small children begin to eat blubber and liver before they can walk. All these foods are exceedingly rich in vitamin D. We are therefore justified in concluding that the antirachitic substance, provided it is freely taken, will prevent rickets in children even though living in insanitary environments and with a scant supply of ultraviolet rays. We have other evidence of the potency of vitamin D in the prevention of rickets. Hess, and others, have shown that many foods containing cholesterol and sterols can be so activated by irradiation with ultraviolet rays as to prevent rickets in an animal on a diet that is ordinarily rachitic producing. Powdered milk, dried brain tissue and yeast are particularly favorable foods to activate and if properly stored will retain their potency for six months. Many vegetables contain phytosterol, the counterpart of cholesterol in animal foods, which also can be activated by the ultraviolet ray and therefore utilized in the prevention of rickets. Carrots and spinach retain their activity after they are cooked, but are not nearly as potent as milk, eggs, brains, liver, yeast and animal fats. Fruits, cereals and starches contain so little sterol that irradiation does not render them effective antirachitic agents, according to Hess.

Three percent cholesterol in olive oil after activation by the mercury quartz lamp is very efficient in curing rickets. Activated cholesterol may be used to fortify cod liver oil, but strange to relate, irradiation of the latter does not increase its potency; on the contrary, it appears to lessen it. Hess has found that irradiation of pure cholesterol is ineffective, apparently it must contain an impurity in order to be activated. Recently this diligent investigator has reported a sterol—known as ergosterol—as the most potent antirachitic substance known. It is so powerful that he thinks it may be the antirachitic vitamin. Activated ergosterol is 500 times as potent as irradiated cholesterol. Five mg. is about the equivalent of one liter of cod liver oil and .0001 mg. daily will prevent rickets in a rat on a rachitic diet. It is believed to be the constituent of cholesterol, sterols and foods that are activated by irradiation with ultraviolet rays. As far as I can ascertain it has not been used in the clinic in the pure state. Irradiated yeast from which ergosterol may be extracted is one of the forms in which it has been administered.

Gerstenberger states the ingestion of cod liver oil by the mother will not

prevent or cure rickets in her breast-fed child, that is, the antirachitic factor in cod liver oil is not transferred to the infant through the milk. On the other hand, if the mother herself is irradiated with ultraviolet rays her breast-fed infant will not develop rickets, or if sick will be cured. It would be logical to infer, therefore, that the vitamin activated by the ultraviolet ray is secreted in the milk or is much more powerful than that found in cod liver oil.

Before considering how the tropics influence rickets, a few remarks as to climatology, solar radiation and ultraviolet rays are essential.

Most tropical climates have a wet and dry season. The humidity is invariably high during the wet period, and in places is relatively high during many of the dry months. In the tropical zone the length of the day does not vary much between winter and summer. In Panama and Manila for example, the sun sets between 6:15 and 6:45 P. M. throughout the year. When the sun is vertical or even approximately overhead as it is at midday during the summer months in temperate climates, the solar rays transverse a minimum of the earth's atmosphere and comparatively few are absorbed; therefore, the heat, light and ultraviolet rays are commonly said to be hot, bright and intense.

Early in the morning or late in the afternoon the rays reach the surface of the earth at a tangent or nearly so, and consequently, many of them are filtered out by the atmosphere and are weak or few in number.

In the tropics at midday the sun is always approximately overhead, therefore the rays are always intense at this time, provided the sky is clear. In temperate zones at the noon hour during the winter months the sun's rays are oblique and hence never powerful.

In mountainous districts even in temperate climates the atmosphere is less dense than at sea level and fewer rays are filtered out.

Other factors influence the intensity of the sun's rays, namely: humidity, smoke and dust.

The number of sun spots are said to influence the quantity of solar ultraviolet rays given off but as they are not subject to our control and as I have not the qualifications, I will not discuss this feature further.

Heat rays (760 millimicrons in length) constitute 60% of solar radiation, visible or light rays (760 to 380 millimicrons) 40% and ultraviolet rays (313 to 290) less than 1%. The shorter the ultraviolet ray the more effective it is as an antirachitic agent. Ultraviolet rays generated by the mercury quartz lamp are much shorter than the solar rays and therefore more potent, some authorities estimate 30 times as powerful.

Dorno estimated that at Davos, Switzerland, the content of midday sun in ultraviolet rays for the month of January is only 10% of that for July. At the same time the short potent rays (296 to 290 millimicrons) failed to reach the earth's surface during midwinter.

At the latitude of Toronto, Canada, Tisdell and Brown ascertained that the sun's rays for the winter months have only a slight antirachitic effect, but a sharp increase took place in March, and

in May they were eight times as strong as in January. In their opinion this great difference is due more to the absorption of the short potent rays in the winter months than to a material reduction in number.

The term skyshine is used to designate the sun's rays reflected from the sky and clouds in contradistinction to the rays received directly from the sun. Thus an object on the sunny side of the street receives both direct and reflected rays, while one on the shady side receives only reflected rays (skyshine). An object in the open but covered by a long cylinder with an open end pointed directly at the sun receives only direct rays (sunshine). The antirachitic effect of skyshine, according to Tisdell and Brown is only from one-half to two-thirds as great as sunshine. According to the same investigators sun's rays passed through ordinary window glass have practically no antirachitic effect. Even the special window glass on the market absorbs from 50 to 75% of all ultraviolet rays. In order to obtain material antirachitic effect within a house in temperate climate, the windows must be open and the child placed in the direct rays of the sun.

During a four year residence in New Mexico at an altitude of over 6000 feet the writer saw very few cases of rickets, all of which were of a mild type. In Southwestern New Mexico, the humidity is low, the atmosphere free of smoke, the sunlight intense, and the number of rainy or cloudy days less than at any military station in the United States. The average annual precipitation during my stay was approximately 11 inches. The weather was so mild even during the winter months that most of the people spent the greater part of the day on their porches or in the open. All these factors would tend to give a maximum of solar ultraviolet rays for the latitude concerned.

The morbidity rate of rickets in the tropics is still a moot question. Everyone concedes that it is less frequent than in temperate climates. A colonial health officer of Trinidad reports that he has not met with a single case in twenty four years. Another one from Jamaica states that it practically does not exist on that island. A doctor from Panama writes, "I have yet to see my first case of rickets in the West Indian negro child." Many doctors have expressed the opinion that rickets is less common among the negroes in the tropics than the whites.

With a view of determining the incidence of rickets in the Canal Zone, Panama, I participated in a survey of children between four months and three years of age. Practically all of the white children—100—of that age were surveyed. This series was given a clinical and X-ray examination. The determination of the blood phosphorus level was not made.

A survey of the negro children, on account of the number and other difficulties, was deemed impracticable. Therefore, 100 of this group on admission to the medical service of the hospital were given a careful clinical examination as to the presence of rickets. The children were stripped and special attention paid to the head, thorax, wrist, ankles and costochondral junctions for evidence of enlargement, change of contour, craniotabes, and

beading. Unless a rosary was obvious to inspection, beading was regarded as absent. The fontanelles, teeth, spine and abdomen were all carefully noted. In the white series the mothers were questioned as to restlessness, head sweating, loss of appetite and pallor.

A clinical diagnosis was not recorded unless the child presented a typical rosary, characteristic enlargement of the wrist or ankles or unmistakable curving of the legs or two or more of the following signs: Craniotabes, postural kyphosis with pot belly, tetany or distinctive deformity of the chest.

Of the 100 cases in the white series, five presented typical rosaries or such characteristic enlargement of the epiphyses, that they could be recognized at a glance. Five others presented questionable enlargement of the epiphyses but associated with such pronounced secondary signs as to justify, in my opinion, the establishment of a diagnosis. Six others presented equivocal evidence as to changes in the epiphyses, chest and spine but had delayed dentition, large fontanels, marked restlessness, head sweating, pallor or loss of muscle turgor. This group was treated for rickets but not diagnosticated as such.

The X-ray films of 98 of the white series were examined by Dr. A. F. Hess who reported as follows:

11 Cases very definite rickets
7 Cases doubtful
15 Cases of healed rickets

"If we were to add the cases of active rickets, of suspected rickets, and of healed rickets, we would have thirty-three cases in all which would indicate one-third of the infants had rickets.

This may be somewhat too high a percentage but judging from a considerable experience in this field, I feel that we can be tolerably certain that one-fourth of these children have rickets.

My conclusion is that you have considerable rickets of a mild type in Ancon in spite of the fact that most of the infants are breast fed."

The negro series comprised children admitted to the hospital almost wholly for diseases other than rickets, most of whom were breastfed until one year old. Twelve cases presented definite clinical evidence of rickets, eight cases presented equivocal clinical evidence of rickets. Two of the negro series had typical tetany and three others obvious bowing of the legs. None of the white series exhibited curving of the legs or tetany. I feel confident that if the negro group had been X-rayed that a larger number would have shown evidence of rickets. The figures show that I overlooked a number of cases, especially healed rickets, in the white series, and it is reasonable to assume that I failed to diagnosticate an equal number in the negro group.

In 1903 I examined fifty-two native children in a small town in the Philippines and found that eight had typical evidence of rickets (15%) and five others equivocal signs (10%). In the early days a moderate amount of bowing of the legs was not uncommon in the island of Luzon. Practically all of the infants at that time were breastfed.

In my opinion these figures support the view that rickets of a mild type is much more frequent in the tropics than the literature of the past fifteen years would indicate. Advanced rickets and rachitic deformities are certainly uncommon.

In Panama and the Philippines the food of the average family consists largely of cereals, fruits and vegetables—a diet now known to be poor in the antirachitic factor. A large percentage of the infants are breast fed, not infrequently until the child is fifteen or eighteen months old. In spite of the custom of protracted lactation, supplemental feeding of rice, bread, banana, etc. is started early.

To the best of my knowledge the habits of the Esquimaux, Laplanders and other races in the Arctic Zone are similar as to nursing and early supplemental feeding. There can be no question but that the diet of the native in the tropics is much poorer in the antirachitic properties than that of his brother above the Arctic Circle. On the other hand, the resident of the tropics has a bath of ultraviolet rays nearly every day. Quite obviously the inhabitant of the far north and regions overcast by clouds and fogs, much of the time, has the benefit of few ultraviolet rays to activate the sterols in his system.

From the above it would appear logical to conclude that a resident of the tropics secures his relative immunity to rickets from the quantity and potency of the ultraviolet rays in his environment. On the other hand, it is just as reasonable to infer that the Esquimau obtains his relative immunity as a result of a diet rich in vitamins. The ultraviolet rays influence the incidence of rickets in the tropics both directly and indirectly.

Directly: While most infants are not exposed to the direct rays of the sun frequently until they are able to walk, the majority of them receive a liberal amount of skyshine, (reflected rays) due to the fact that houses in the tropics have ample veranda space, or lacking this, large doors and wide windows that are usually open. As soon as the child is able to walk most of them find the sunshine, provided the mother is not unduly solicitous about the child's complexion.

Indirectly: During the period that the infant is breast fed the mother usually comes in direct contact with the sun's rays several hours a day. Gerstenberger has shown that adequate exposure of the mother to the ultraviolet rays results in the prevention of rickets in her breast fed infant. While I do not know of experimental proof, it is certainly logical to assume that milk from cows and goats in the tropics is likewise rich in the antirachitic substance. All food that grows above the ground and that contains sterols should be activated by the sun's rays. It is true, however, that many of the tropical foods are poor in cholesterol and that only a few as spinach, cabbage, etc., are thin enough to be penetrated by the ultraviolet rays; therefore, the practical benefit from the activation of food by the sun is probably slight. At first blush it would appear that rickets should never occur in the tropics. How, then, do we account for the fact that about 25% of the children develop it, albeit in mild form? Most tropical countries and all

that I am familiar with, have two season—wet and dry. The wet season usually comprises from seven to nine months of the year. During this period the humidity is high and there are many cloudy and partially cloudy days. Obviously when the sky is overcast with clouds few if any ultraviolet rays reach the earth's surface. Humidity during the wet season often approaches the saturation point. Physicists tell us that high grades of humidity obstruct many ultraviolet rays. Some women, particularly the newcomers to the tropics, rarely venture out of the house during the heat of the day and likewise would consider it unjustifiable, if not criminal, to permit their infants to bask even in the reflected rays of the sun. I venture the prediction that as soon as the important factors relative to the etiology of rickets become common knowledge that this prevalent disorder of nutrition will disappear from the tropics, except in those parts that have a protracted wet season, excessive number of cloudy days—or what is equally deplorable old fogy parents who are not amenable to reason.

Summary

1. About 25% of children in the tropics have rickets. The disease is usually of a mild type. Severe rickets and marked rachitic deformity are rarely observed.

2. Long wet seasons—and high humidity favor the development of rickets.

3. Diet poor in sterols is a less important factor.

4. Proper knowledge by the layman in the tropics of the etiology of rickets should result in the practical disappearance of the disease in all but the cloudiest areas.

A Study of the Variable Factors in the Use of the Wright's Stain*

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DURING the last three years, while engaged in collecting and staining blood smears in quantity to be used in demonstrating to students the various pathological conditions of the blood, we have experienced considerable difficulty in obtaining constant results with the Wright's Stain as employed in the usual way. In trying to eliminate these variations we have studied the results obtained from various aspects and the following outline will illustrate most of the factors responsible for our failure to obtain uniform stains.

Difficulties Which Must Be Controlled

In a large number of cases defects in staining are due to lack of familiarity with the conditions which must be controlled in order to produce satisfactory stains, just as it was in our case before we began this study.

Conditions Which Must Be Controlled

I. *In regard to the blood smear*:
   1. Glassware. (Must be free from acid, alkali, grease, and dirt.)
   2. Thickness of Blood Smear. (Too thick: crenation during drying; poor fixation with methyl alcohol of stain.)

II. *In regard to the stain itself*:
   1. Quality of pigment.
   2. Concentration of pigment in staining solution. (Too concentrated — overstains red; too dilute—understains.)
   3. Quality of alcohol. (Unless almost 99%, red cells are poorly fixed—distorted and vacuolated.)
   4. Quality of water. (Acid water—stain too red; alkaline water—too blue; impurities—precipitated stain.)
   5. Proportion of water to stain. (Too little water—precipitated stain; too much—understaining).
   6. Staining time. (Usually varies with each new batch prepared.)

III. *In regard to personal factors*:
   1. Due to forgetfulness or distractions:

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(a) Allowing stain to dry on slide.
(b) Incorrect timing.

2. Due to bungling or accidents:
   (a) Allowing stain to run off slide.
   (b) Failure of diluting water to spread evenly.
   (c) Wrong proportion of water to stain.

It can be easily understood that when we have to run the gamut of so many chances of failure there is little wonder that we often manage to spoil a good number of slides when we attempt to stain a number at a time.

In our experience the outstanding factors responsible for failures were those given under the heading of personal factors. With this in mind we set out to modify the usual procedure so that as many of these factors as possible might be eliminated. It occurred to us that purposely overstaining smears and subsequently partially decolorizing them might be helpful. This required the devising of a satisfactory destaining solution.

We had already made use of the common expedient of treating overstained preparations with ethyl alcohol, but it is exceedingly easy to entirely decolorize the smears with alcohol. We experimented with many other common laboratory solvents, but found none of them even as satisfactory as the alcohol. Some of them failed to dissolve any of the stain, others removed it entirely.

We then attempted to find some substance which added to the alcohol would slow the action and make it more differential. Since the blues were quickly removed we tried adding ordinary methylene blue, which did in fact have some of the action desired, but was far from satisfactory. Wright's stain itself was then tried, and it was discovered that alcohol saturated with this pigment, quite paradoxically, removed a great part of the excess stain but left the nuclei of the leucocytes quite distinct. Anything less than saturation, however, failed to slow the action of the alcohol and preparations were quickly decolorized.

An article describing this new procedure will appear in a forthcoming issue of the Journal of Laboratory and Clinical Medicine, but it may be of interest here to say a word or two in regard to the preparation of the solutions and the method of applying them.

Since two solutions are necessary we have designated them Solutions I and II. Solution I is prepared by saturating absolute methyl alcohol with Wright's Stain (about 0.3 gm. per 100 cc. of alcohol) by allowing to stand for 24 hours, or longer, with occasional shaking. It is then filtered and diluted with one-fifth of its volume of methyl alcohol.

Solution II is prepared by saturating ethyl alcohol (85-90%) with Wright's Stain (about 0.2 gm. per 100 c.c. of alcohol) by allowing to stand for 24 hours, no longer, with occasional shaking. It is then filtered into a dropping bottle as used.

The procedure of staining is as follows:

1. Pour on just enough of Solution I to cover smear; *drain off excess stain* immediately. Let

stand until stain remaining *turns red.*

2. Cover slide with buffered water; let stand for one minute or longer.
3. Wash with Solution II until most of the red precipitate on the slide disappears.
4. Wash with buffered water, dry, and examine.

A little experience with this new procedure will demonstrate that a number of the errors due to personal factors are eliminated. In the first place, drying at any stage *after draining off excess stain* does not materially harm the preparation, which in itself is a marked advantage. Forgetfulness and distraction are much less likely to result in ruining smears, since they can be left standing almost indefinitely at any point in the procedure and the stain completed when you come back. Likewise there is less opportunity for bungling and accidents to play a part. No doubt all of you have had your Wright's stain run off over the edge of your slide, and continue to do so even when you add more, which completely upsets your calculations as to how much water should be added, and also usually means that a part of the slide has had the stain dry on it before the minute of application has passed. Moreover, I am sure that everyone has experienced difficulty in getting the diluting water to spread rapidly over the slide in staining by the usual procedure, and any part not covered by water almost immediately will be covered with precipitated stain. These difficulties are avoided in the new procedure.

In our experience, and in that of others who have been kind enough to test out our procedure, much more uniform results are obtainable, not only because of the minimizing of the influence of personal factors, but also because of certain inherent advantages in the procedure itself. The staining time is of considerably less importance. Nuclei are almost as deeply stained within one minute after the water is added as in longer times. Less than a minute, however, usually fails to stain sufficiently.

The proportion of water to stain has no influence, since an excess is always added.

There is no overstaining of preparations, as all excess stain is removed by Solution II.

It is likewise of considerable interest to note that the control of a few major factors assures great constancy in staining. Taking it for granted that those who stain blood smears can prepare good thin smears on properly cleaned glassware, we believe that the proper control of four major factors will insure uniformity.

The first factor, and one of the most important ones, is the reaction of the water used. Using water buffered with phosphate solutions we find that the colors which we prefer are obtained when the water is a pH of 6.4 to 6.8. The colors are fairly satisfactory for differential counting with a pH as low as 5.6, but the erythrocytes are very pink and the nuclear blues of the leucocytes are hazy and indistinct. On the other hand, when the pH goes beyond 7.4 the red cells

take on a greenish blue hue and the granules and nuclei of the leucocytes fail to take the eosin and azure properly.

Distilled water is usually slightly acid and consequently makes a satisfactory diluting and washing medium without buffering. However, the amount of acid is subject to variation, especially where the water is distilled from city supplies which are chemically treated. For this reason we prefer to use a water which is buffered.

A simple method of preparing such a water is to keep on hand 1% solutions of KH_2PO_4 and Na_2HPO_4. Usually 30 c.c. of the former and 20 c.c. of the latter added to a liter of distilled water will give about the proper reaction. If the erythrocytes stain too pink more of the sodium phosphate can be added, if not pink enough, more of the potassium is added.

A second important factor to be controlled is the percentage of ethyl alcohol used in preparing Solution II. The best strength is 85-90%. Stronger alcohol often fails to remove the red precipitate left in overstaining the smear and also tends to make the erythrocytes pinker. Weaker alcohol removes both reds and blues, even to complete decolorization.

A third factor is the concentration of the pigment in Solution I. It often happens that a stain loses considerable alcohol by evaporation, thereby becoming concentrated. Such a solution will cause overstaining with eosin. On the other hand, too dilute a solution will cause understaining or bluish color to predominate.

The fourth factor is the staining time, which, though of less importance than in the usual procedure, must be controlled within certain rather wide limits. Less than a minute of staining after the addition of water usually means understaining, while an exceedingly long time will cause an overstaining with red.

Every method will have certain points which some will consider disadvantages, and this is true of this procedure. One point is that there are two solutions, instead of one, to be prepared and used, and this is a fairly large objection in the minds of some.

Another is that thinner smears must be used on account of the short exposure of the preparation to the methyl alcohol of Solution I, which is not sufficient for proper fixation of the erythrocytes in thick smears.

A third point is the fact that the stains obtained are much more delicate. Those used to the dense and opaque nuclei often resulting from slight overstaining by the usual procedure depreciate the more delicate colors of the nuclei and granules of the leucocytes. Personally we prefer the colors obtained by this procedure because we feel that we can see more structure in the cells and the differentiation of the various kinds of leucocytes is as clear-cut, if not more so, than with the ordinary Wright's stain.

Not only do we feel that normal structures are well delineated but pathological conditions are also well demonstrated. The delicate tints of the erythrocytes bring out clearly the basophilic stippling occurring in the various anemias and also the poly-

chromatophilia or diffuse bluish staining of certain red cells usually accompanying the stippling.

Malarial parasites are beautifully stained, and the various structures are distinctly discernable. Schueffner's dots show up very plainly in tertian malaria.

The pathological leucocytes and erythrocytes of the anemias and leukemias are also well differentiated, the granules of the various myelocytes taking on very characteristic colors.

A very convenient summary of this study will be to rearrange the points discussed into an outline for eliminating defects in staining with the two solution Wright's Stain. It follows:

I. Intercellular or Pericellular Stain (Bluish or Pink)

1. Improperly washed slides.
2. Too concentrated Solution I.
3. Too short application, or uneven application, of Solution II.

II. Granular Precipitate Over Smear:

1. Granules of dried stain from mouth of staining bottle.
2. Allowing stain to evaporate before draining off excess.
3. Improperly washed slides.

III. Predominance of Red:

1. Water too acid.
2. Solution I too concentrated.
3. Solution II made with 90%, or higher, ethyl alcohol.
4. Staining time too long.
5. Pigment contains too much eosin.

IV. Predominance of Blue:

1. Water too alkaline.
2. Solution not concentrated enough.
3. Solution II made with less than 85% ethyl alcohol.
4. Staining time too short.
5. Pigment contains too much polychromed methylene blue.
6. Smears too old. (Over a few weeks old—difficult to stain)

V. Stain Pale:

1. Staining time too short.
2. Solution I not concentrated enough.
3. Solution II not saturated with pigment.

VI. Vacuolated or Distorted Erythrocytes:

1. Smears too thick.
2. Smears dried too rapidly.
3. Methyl alcohol (Solution I) contains too much water.

Editorial

POSSIBLE RELATIONSHIPS BETWEEN PAROTID AND PANCREAS

Because of certain anatomical and physiological similarities between the salivary glands and the pancreas, as well as the common involvement of both organs in certain affections, there has long existed a well-defined scientific curiosity as to the possibility of functional inter-relationship between them. As early as 1890 the Italian school based such a belief upon the work of De Renzi and Reale who had demonstrated experimentally the occurrence of glycosuria in dogs after the removal of the duodenum and the salivary glands, the pancreas being left in the body. These workers concluded that the salivary glands had a specific function aside from the production of saliva. This view was opposed by Minkowski who regarded the glycosuria in this experiment as a transitory one, and not comparable in degree to that shown by him to follow the total extirpation of the dog's pancreas. Nevertheless, numerous writers felt that the question was still an open one, and the idea persisted that there might be other organs or tissues concerned in the sugar metabolism besides the pancreas. If such were true, then these other organs might compensate for the pancreas when its function was lowered. In 1893, A. Seelig advanced the hypothesis that by gradual suppression of the pancreatic function glycosuria might not take place because of the compensatory activities of other organs. In 1906, another Italian worker, Italia by name, demonstrated the occurrence of parotid hypertrophy following experimental atrophy of the pancreas, as well as the reverse production of pancreatic hypertrophy following experimental extirpation of the salivary glands. Recently this question has been attacked anew from an entirely different angle, that of blood-sugar estimations, and during the last year a number of investigators in different parts of the world have been working independently along this line, and have come to similar conclusions. Goljanitska and Snairnowa have attempted the surgical treatment of diabetes by parotid ligation and transplantation of portions of the submaxillary gland. They ascribed a definite therapeutic result to this surgical method. Utimura found that extirpation of the parotid glands in dogs led to a permanent lowering of the blood-sugar, followed by a gradual numerical increase in the islands of Langerhans in the pancreas, and an increase of the glycogen content of the liver parenchyma. This same investigator found also that there existed an antagonistic relationship of the submaxillary gland towards the parotid. Mansfield also found that the experimental

cutting out of the parotid by means of the ligation of Stensen's duct produced the same depressant effect upon the blood-sugar of the dog. More recently S. Seelig has reported the results of similar experimental work as to the effect upon the blood-sugar of dogs by the suppression of the external secretion of the parotid. He first investigated the effects of parotid ligature upon the hyperglycemia of dogs with pancreatic diabetes, and found that the suppression of the external secretion of the parotid had no effect upon the hyperglycemia in the dog following total pancreas extirpation; the animals died with the characteristic diabetes cachexia. A second series of experiments was then carried out in which after a preliminary proving of the fasting blood-sugar for a number of days, the parotid duct was first ligated, and then after several days the total extirpation of the pancreas was carried out. From this series of experiments it appeared that the total extirpation of the pancreas following parotid ligature did not lead to such high blood-sugar values, as when it is carried out without parotid ligation. Further, the dogs showed a better healing of the wounds, and did not develop the characteristic rapidly progressive cachexia of pancreatic diabetes. Another series of investigations was concerned with the study of the fasting blood-sugar in dogs in whose Stensen's duct alone had been ligated. The state of the blood-sugar was observed, and the functional regulation tried out by the administration of adrenalin and glucose. Following the operation there developed in one to two days a stasis-tumor of the cheeks which declined after five or six days. The animals showed a marked hunger, rapid loss of weight and fatigability. The testing of the blood-sugar regulating function by means of adrenalin and glucose showed a slight hyperglycemia in the dogs with parotid ligatures, as well as in dogs not so treated. Insulin susceptibility was also tested; the convulsion threshold was found to be lower in the ligated dogs than in normal animals. The functional proving was not, however, carried out in a sufficiently large number of animals, and the author offers these results with reservations. The histological study of the parotid, liver and pancreas of these cases was also not completed, and will be reported later. Since January, 1928, ten diabetic patients have been treated by means of parotid duct ligation in Sauerbruch's clinic, by means of a special technic devised by Gohrbandt. They were in part moderately severe cases and in part severe. It is yet too soon to speak definitely of the results in these cases. Seven appear to have been favorably influenced as far as the symptoms of blood-sugar, urine-sugar, acidosis and furunculosis were concerned. Three cases remain unaffected; they will be reported upon later. It should not be necessary to state that this operation is only in the experimental stage, and should not at this time be regarded as having a general application in the therapeusis of diabetes mellitus. The final conclusions and judgment of the results of this operation will be given in a later publication. At the present time any judgment as to the practical value of this work must be withheld.

The results of these different investigations as to a possible functional relationship between the parotid and pancreas are extremely interesting. They serve to support the old ideas promulgated by the Italian workers of the last decade of the last century, and various clinical surmises that have since been made. Many interesting observations have been reported from time to time of pancreatic involvement in epidemic parotitis. Acidosis and glycosuria have been observed to occur at the peak of an attack of mumps, and the question arises as to whether these symptoms are due directly to the disturbed function of parotid and submaxillary glands or to autoinfection of the pancreas with consequent functional disturbance. A number of writers have emphasized the not infrequent complication in mumps of a benign form of pancreatitis with symptoms of abdominal pain, vomiting and palpable pancreatic tumor. Sugar may appear in the urine; and some cases of well-defined diabetes have been thought to have their origin in a pancreatitis complicating mumps. There are, therefore, a number of recorded observations bearing upon the question of parotid and pancreas interrelationships; recent experimental work seems to be drawing these towards a focussing point. Further experimental work along this line will be awaited with great interest.

HEALTH OF WORKERS IN DUSTY TRADES

The United States Public Health Service has completed a study of the health of workers in a Portland cement plant, the first of a series covering the dusty trades, according to an announcement recently made by Surgeon General H. S. Cumming. The study was undertaken to ascertain whether persons working in an atmosphere containing numerous minute particles of a calcium dust suffered any harmful effects. The investigation was conducted in one of the older, dustier plants, so that the effect of large quantities of the dust could be observed. Records of all absences from work were kept for three years, and the nature of disabling sickness was ascertained. Physical examinations were made, X-ray films taken, and the character and amounts of dust in the atmosphere of the plant were determined.

The results of this investigation indicated that the calcium dusts generated in the process of manufacturing Portland cement do not predispose workers to tuberculosis nor to pneumonia. The workers exposed to dust experienced, however, an abnormal number of attacks of diseases of the upper respiratory tract, especially colds, acute bronchitis, diseases of the pharynx and tonsils, and also influenza or grippe. Attacks of these diseases serious enough to cause absence for two consecutive working days or longer occurred among the men in the dustier departments at a rate which was about 60 per cent above that of the men in the comparatively non-dusty departments. Limestone dust appeared to be slightly more deleterious in this respect than cement dust.

Outdoor work in all kinds of weather such as was experienced by the

quarry workers appeared to predispose to diseases of the upper respiratory tract even more than did exposure to the calcium dusts. In the outdoor departments of the plant, also, the highest attack rates of rheumatism were found. The study also indicated that work in a cement dusty atmosphere may predispose to certain skin diseases such as boils, to conjunctivitis, and to deafness when cement dust in combination with ear wax forms plugs in the external ear. When the dust in the atmosphere is less than about ten million particles per cubic foot of air it is doubtful that the above-mentioned diseases and conditions would be found at greater than average frequency.

Modernization of plants and installation of ventilating systems are helping to solve the dust problem of the industry.

PUBLIC HEALTH IN FLOODED AREA OF MISSISSIPPI VALLEY

Approximately one year has elapsed since the frightful disaster of the flood in the Mississippi Valley. The United States Public Health Service states that some comfort may be obtained in the knowledge that better communities are being builded on the ruins of those destroyed, and as a rule, a better public health regime has been inaugurated. Following the flood of waters there has developed another flood—a flood of sanitation development, which has placed that area many years ahead of the old program in connection with the development of full-time county health service. Since July, 1927, 78 counties have joined the roll of those that are enjoying adequate public health protection through the labors of over 300 full-time health workers. This is a distinct step forward, and a stimulus to perpetuate these endeavors.

If the work continues as it has to date, the Mississippi Valley will soon enjoy the universal public health protection it deserves.

This should serve as a splendid example to other communities and stimulate them to strengthen their local health departments and secure adequate full-time health service.

Abstracts

Emetin—Its Effect on the Rabbit's Heart. By PHOEBUS BERMAN and WILLIAM H. LEAKE (Research Prize Essay of the California Medical Association for 1928. California and Western Medicine, June, 1928, Vol. XXVIII.)

Myocardial failure associated with the therapeutic use of emetin is not unknown, and probably occurs more frequently than the reports indicate, as emetin and its salts are widely used in the treatment of amebiasis and other protozoan infections. The literature contains only a few articles dealing with the effects of emetin on the heart. It was thought, therefore, that an electrocardiographic study of the effect of emetin on the rabbit's heart might reveal interesting findings. Such an investigation was carried out, with the following results: In rabbits, emetin hydrochlorid given intravenously in doses between one and two mg. per pound body weight will produce a distinct ventricular tachycardia which will revert to a normal rhythm in about ten minutes. Digitalis in the form of digifolin will produce no definite change in the electrocardiogram of a rabbit when administered intravenously in very large doses. Emetin hydrochlorid given in conjunction with a relatively small amount of digitalis (digifolin 1 cc.) will not produce a definite change in the electrocardiogram unless the dose of emetin is between one and two mg. per pound body weight. In other words, digitalis will not lessen the dose of emetin required to produce definite changes in the electrocardiographic record. The minimal intravenous lethal dose of emetin hydrochlorid for a rabbit is about 2 mg. per pound body weight. The electrocardiogram of a rabbit receiving a lethal dose of emetin hydrochlorid shows a ventricular fibrillation from which, in their experiments, the animals did not recover. Daily intravenous injections of emetin hydrochlorid approximately equivalent to 1 mg. per pound body weight produce no marked permanent changes in the electrocardiogram of rabbits receiving a total amount of 18 mg. and 28 mg. respectively. An electrocardiogram of a rabbit dying of sodium cyanid is given for purposes of comparison.

An Investigation to Determine a Satisfactory Standard for Beriberi-Preventing Rices. By EDWARD B. VEDDER and T. R. FELICIANO (The Philippine Journal of Science, April, 1928, p. 351).

Although medical authorities still differ with regard to a number of details concerning the etiology of beriberi, there is a very general consensus of opinion to the effect that beriberi is a deficiency disease, produced whenever, in the absence of an adequate mixed diet, highly milled rice is used as the main food staple, and that the disease can be prevented by the substitution of a sufficiently undermilled rice. In the case of the Philippine Scouts, when supplied with the best grade of highly milled rice, during the years 1902-1909, the incidence of beriberi was often as high as 10 per cent of the entire number (5,000). Since 1910, when undermilled rice was substituted, beriberi has been eradicated among these troups, although they were living in the midst of a population where beriberi is very common. Such experiences led several sanitary authorities to recommend legislation by the various countries most concerned which would diminish the production or importation of highly milled rice, but it was promptly realized that no such law could be administered without a satisfactory legal standard for beriberi-preventing rices. Beriberi cannot be eradicated without legis-

lation in the countries in which it is endemic, and legislation waits on the determination of a satisfactory standard for beriberi-preventing rices. Accordingly this investigation was begun in 1925, and completed in 1927, and the following conclusions were drawn. The chemical index proposed for beriberi-preventing rices is: Any rice having 1.77 per cent of phosphorus pentoxide plus fat, but not less than 0.4 per cent phosphorus pentoxide; or any rice having not less than 0.62 per cent phosphorous pentoxide and with at least 75 per cent of the external layers of the grain remaining. No rice possessing these requirements was found to produce polyneuritis in pigeons, and this standard excluded only nine rices out of two hundred that afforded protection to pigeons. Since pigeons are so much more susceptible to the deficiency of antineuritis vitamin than is man, and since man seldom lives on rice alone, a standard that will protect pigeons will not only protect man, but will also provide a factor of safety. This factor of safety is a necessity if beriberi is to be eradicated, because defects in the storage of rice or in its preparation for food may materially reduce its vitamin content. Of ten rice samples tested, thorough washing reduced the phosphorus pentoxide content from an average of 0.447 to an average of 0.197 per cent. Presumably the vitamin content was similarly reduced. In an experiment with twenty insect-infested rices stored for one hundred days, an average total of 2.61 per cent (fats phosphorous pentoxide and ash) was reduced to 1.71, and seven undermilled rices that should have prevented polyneuritis were converted into highly milled rices that produced polyneuritis. It is, therefore, highly probably that the loss of vitamin during long storage of undermilled rice is caused by the depredations of insects that eat the external layers of the grain.

Zur Frage der toxischen Synthalin—Wirkung bei diabetischen Kinder. By H. Hirsch-Kauffmann and A. Heimann-Frosien (Klinische Wochenschrift, July 1, 1928, p. 1272.)

Fifteen diabetic children have been treated systematically with synthalin for over a year, and it has, therefore, been possible to make a more accurate judgment as to the effect upon the carbohydrate tolerance of the peroral use of this anti-diabetic remedy and as to the toxic effect upon the child's organism of its protracted use. As these writers have previously emphasized, an effective synthalin therapy is possible only by correct dosage more than one and a half mg. of synthalin per kilogram body-weight must not be given; they advise one mg. per kilogram body weight. Higher dosages produced constantly bad results. A pure synthalin therapy is possible only with patients whose glycosuria is not too high (20-30 g.). In such cases it has been possible to treat children six to twelve years of age for a year without insulin on the mixed diet recommended previously by these authors, not only in the Clinic but also ambulatory cases. The children attended school and showed normal development, both as to weight and increase in height. No permanent injury resulting from the treatment was observed. The temporary appearance of slight glycosurias as the result of infections lowering the tolerance could not, however, be avoided by the synthalin treatment. While in such cases treated by insulin it is possible by careful increase of the dose to control the glycosuria, it is not possible to do this with synthalin because of the production of unpleasant symptoms, such as loss of appetite, vomiting, etc. Under such circumstances, as in the pre-insulin period, the child must be brought into a metabolic equilibrium by a temporary limitation of the diet, especially of the carbohydrates. In this way the authors were able to bring their diabetic children through mild colds, otitis, and even a more severe epidemic of mumps. It was observed also that synthalin treatment produced an insulin resistance, so that larger doses of the latter were needed to produce an aglycosuria. This resistance is apparently relative, since in further treatment with insulin the dose could be reduced. It is also possible that the use of synthalin makes larger quantities of car-

bohydrates utilizable to the organism, so that after its discontinuance larger doses of insulin are required to meet this increased utilization. As to toxic effects produced by this guanidin preparation, occasional vomiting, temporary loss of appetite, and abdominal pains were the only symptoms observed; these were not serious and disappeared spontaneously. In one case icterus appeared and the synthalin treatment was discontinued. The significance of this case could not be determined. It has been assumed that synthalin had an injurious effect on the liver; on the other hand icterus is not a rare complication of diabetes, or it may have been an ordinary catarrhal jaundice. In both insulin- and synthalin-treated cases of diabetes there is an occasional urobilinuria, but no striking increase of icterus in the synthalin-treated cases has been observed. The authors do not regard their case as indicating a hepatic injury due to the treatment; the child quickly recovered and gained three pounds in weight, so that there could have been no permanent liver damage. They conclude from their year's experience with this drug that synthalin aids in the treatment of diabetes in children. Even though it cannot completely replace insulin, it works especially well in combination with insulin. With its use the need for insulin is so lowered that one injection daily of the latter may suffice; in this way a great saving of insulin is effected. Of greater importance is the fact that with synthalin treatment hypoglycemic reactions, the most unpleasant results of insulin treatment, occur much less frequently as the result of the combination therapy. There are juvenile diabetics whose daily needs for insulin vary so greatly, that in spite of the most extreme precautions there may be multiple occurrences of hypoglycemia in a single week. For such cases synthalin becomes an adjunct of greatest service. Since synthalin does not wholly meet the therapeutic requirements scientific investigations must be continued until some preparation is produced whose use will be unattended by symptoms, and the necessary doses of which can be given to any diabetic without consideration of possible harmful results.

Zur Pathogenese der gastrogenen Tetanie. By HERMANN STEINITZ (Klin. Wochenschr., May, 1928, p. 932.)

Gastrogenous tetany is a rare disease. In the cases that have been observed throughout the world many causes have been advanced in its explanation. These may be divided into five groups: concentration of blood due to loss of water; reflex action; autointoxication; loss of chloride; and alkalosis. In the last few years the discussion has limited itself more and more to the three last named hypotheses. During a short period recently two cases of typical gastrogenous tetany were observed in the Strauss Clinic in Berlin. One of these was a case of pylorus stenosis caused by a parapyloric ulcer, the other a low lying duodenal stenosis due to a carcinoma of the duodenojejunal flexure. In both of these cases the blood studies showed a normal refraction index towards the upper limit of a slightly increased one; a normal potassium and calcium picture; a negative N balance in one case, and a slightly increased residual N value in the other; extreme high values for the alkali reserve; very low blood-chloride and almost chloride-free urine, marked chloride retention; a lowering of the formerly hyperacid stomach contents to an acidity with very low chloride values. In both cases the extremely low chloride deficiency of the organism, due to the excessive vomiting, appeared to be the decisive, at least the exciting factor, in the origin of the tetanic phenomena. Certainly in these two cases the loss of chloride appeared to be of essential significance for the occurrence of gastrogenous tetany. The question naturally arises as to the mechanism operating in these cases. Only a relatively small number of cases of pyloric stenosis develop tetany. Why does tetany practically never develop in association with the pylorus spasm of infants, although the same symptoms of acid vomiting, hyperchloremia, hypercapnia, partly decompensated alkalosis, etc., occur in this condition, as in the case of pylorus stenosis in adults? It ap-

pears that something more is necessary—a certain disposition—in the form of tissue- or blood-changes of a tetanogenic character. Changes in the parathyroids are at once suggested. The experimental and postoperative parathyreoprival tetany is, of course, well known, but for other forms of tetany parathyroid changes and their significance are still disputed. In some cases of gastrogenous tetany anatomical changes in the parathyroids have been demonstrated; in other cases, as in the two of Steinitz, no such changes are found. Such negative findings do not, however, exclude the possibility of functional changes. In one of Steinitz's patients "'softening and crumbling" of the teeth had been noted at puberty coincident with the beginning of stomach symptoms; this might be an indication of parathyroid insufficiency. It is well known that such a disturbance may be for a long time latent, until brought to manifestation through toxic irritation or a change in the ionic equilibrium. It is possible that gastrogenous tetany is a relative parathyroid insufficiency, whereby the chloride loss becomes the exciting moment for the production of tetany.

Reviews

Modern Medicine. Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F. R. S. Third Edition, Thoroughly Revised. Re-edited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia, Fellow of the Royal College of Physicians, London; Formerly Associate Professor of Medicine, The Johns Hopkins University. Assisted by Elmer H. Funk, M.D., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. Vol. VI, Diseases of the Nervous System—Diseases and Abnormalities of the Mind. 964 pages, illustrated. Lea and Febiger, Philadelphia, 1928. Price in cloth, $9.00.

This is the final volume of the third edition. Its contributors include Barker, Spiller, Russel, Bramwell, Collins, Cushing, Hunt, Thomas, Taylor, Holmes, Buzzard, Clark, Burr, Jelliffe, McCarthy, Sachs and Strecker. The contents consist of two parts, the first on Diseases of the Nervous System, the second on the Diseases and Abnormalities of the Mind. Part II is written wholly by Edward A. Strecker, while the other authors mentioned above have collaborated on Part I. The introduction is by Barker, diseases of the motor system by Spiller, combined diseases of the spinal cord by C. K. Russel, sclerosis of the brain and diseases of the meninges by Edwin Bramwell. Joseph Collins has written the sections on topical diagnosis of diseases of the brain and aplasia; Harvey Cushing those on intracranial tumors and hydrocephalus. Ramsay Hunt has revised Southard's chapter on acute encephalitis and brain abscess and written the one on epidemic encephalitis. Henry M. Thomas, Jr., has revised the section on diseases of the cerebral bloodvessels. The chapter on diseases of the cerebral nerves has been written by E. W. Taylor and that on the peripheral nerves by G. M. Holmes. The diffuse and focal diseases of the spinal cord is by Buzzard and Symonds of London. L. P. Clark is the contributor of the section on epilepsy and C. W. Burr of that on the traumatic neuroses and psychoses. The two sections on hysteria, the migraines, neuralgia, professional spasms, occupation neuroses and tetany are by Smith E. Jelliffe. The three sections including paralysis agitans, chorea, choreiform affections, infantile convulsions, myasthenia gravis, paramyoclonus multiplex, periodic paralysis, astasia-abasia and adiposis dolorosa are by Daniel J. McCarthy. Syphilitic diseases of the central nervous system and amaurotic family idiocy are contributed by B. Sachs. This volume seems to the reviewer to be the best one of the third edition. It is well brought up to date, and includes good presentations of modern views of the diseases of the central nervous system. In itself this volume constitutes an excellent textbook on diseases of the nervous system; and it is especially adapted to the uses of the internist who will find in it our knowledge of this subject so arranged that it will answer his immediate clinical needs in diagnosis.

Modern Methods of Treatment. By Logan Clendening, M.D., Associate Professor of Medicine, Lecturer on Therapeutics, Medical Department of the University of Kansas; Attending Physician, Kansas City General Hospital; Physician to St. Luke's Hospital, Kansas City, Missouri. With chapters on Special Subjects by H. C. Anderson, J. B. Cowherd, H. P. Kuhn, Carl O. Rickter, F. C. Neff, E. H. Skinner and E. R. DeWeese. Second Edition. 815 pages, 96 illustrations. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, $10.00.

The many changes in therapeutics of the last five years have made the revision of this book necessary. The Minot-Murphy diet in pernicious anemia, the scarlet fever antitoxin, the parathyroid hormone, the ovarian hormone, ephedrine sulphate, novasurol and ammonium chloride in edema, the malarial treatment of syphilis, lipiodol instillations in chronic lower respiratory infections, the metabolism of obesity, spirochetal pulmonary infections, the use of peptone in migraine, phenylhydrazine in polycythemia, etc., have necessitated the addition of much new material. The author has also added new sections on antidotes and the treatment of acute poisonings, resuscitation by artificial respiration, and new chapters on the treatment of the chronic intoxications; of the diseases of the organs of locomotion, and of the common diseases of the nervous system. The entire book has been carefully revised. Particularly the chapters on Digitalis, Asthma and Diabetes have been recast. The tenth edition of the Pharmacopeia has been used as a basis for revision of drug nomenclature. About twenty-five new illustrations have been added. The general plan and purpose of the book have not been changed. The author has kept the general practitioner in mind and has endeavored to encourage him to adopt and to use methods which he is likely to believe are effective only in the hands of specialists. There is a large amount of valuable material in this book; but also a large number of methods of treatment so incompletely described that they cannot be of much use to the practitioner. Some of these read as if they were seen only in abstracts, and not in the original article. Take the liver treatment of pernicious anemia, the preparation of liver, amount to be taken, etc., are given, but no word of the regulation of the treatment according to the blood changes, and there is no mention of liver-extract which has been used for over a year. This incompleteness of detail is true of other remedies and treatments advocated. It is not sufficient to mention a therapeutic agent, and to give dosage and possible results. What the practitioner needs are the details of treatment indicating the results, the dangers, and the after-effects. It seems to the reviewer that the book is somewhat lacking in this respect.

The Glands of Destiny. A Study of the Personality. By Ivo Geikie Cobb, M. D., 295 pages. The MacMillan Company, New York, 1928. Price in cloth, $3.00.

This is an attempt to express in a popular style the rôle of the endocrine glands in the formation of the individual personality. As the author states it, what is herein discussed may be called the physical or chemical contribution to the personality, in which contribution the glands of internal secretion play a chief part. The personal equation is determined in part by tangible causes, and in part by other factors more or less abstract. While there are still many gaps in our knowledge of these structures and their functions, enough is now known to warrant a survey of their relationship to that psychological mixture known as the personality. The author realizes the danger in doing this, and hopes that surmise has not outrun its legitimate course in his book. He has attempted to distinguish physiologic facts from assumptions based thereon. After an introductory general discussion of the endocrine glands he takes up each one in turn giving a brief and concise account of what is known of their function and interactions, and the human types associated with pathologic conditions of these glands. Upon this foundation he constructs various hypothetical applications to racial characteristics, the process of aging, civilization and warfare, the internal secretions in everyday life and personality. The author has been unable to resist the temptation to make a little stronger case for his hypotheses than the actually known facts warrant, and the danger is that a non-medical reader may take it all as absolute fact, which it is not. Perhaps this is offset by the important ideas that he will acquire by its perusal.

Syphilis. A Treatise on Etiology, Pathology, Symptomatology, Diagnosis, Prognosis, Prophylaxis and Treatment. By Henry H. Hazen, A.M., M.D., Professor of Dermatology and Syphilology, Medical Department of Georgetown Uni-

versity; Professor of Dermatology and Syphilology, Medical Department of Harvard University; Visiting Dermatologist to Georgetown University Hospital; Freedmen's Hospital. Second Edition. 643 pages, 165 illustrations including 16 figures in color. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, $10.00.

This is the best of the smaller textbooks on syphilis, in that it is brought up to date in the modern knowledge of syphilis, and speaks from an acquaintance with recent literature. It is therefore authoritative. It is not made up of old statements handed down from textbook to textbook for the last fifty years, but presents a thorough and careful analysis of what we have learned of syphilis since the discovery of the spirochete. This enormous mass of information is condensed into a very readable text. Authorities are mentioned with a reference number in the text, and at the end of each section the full reference in the literature is given. This makes the work an exceedingly useful one for the medical student, who can comprehend easily the pithy resumé of the subject, and then be able to look up the original investigations mentioned since the full references are at hand. In many respects the second edition is practically a new book. The chapters on Occurrence and Economic Importance, Syphilis of the Nervous System, Diagnosis, Prophylaxis and Treatment have been entirely rewritten. All of the remaining chapters have been revised, and the most recent bibliography added. New illustrations have been added. These illustrations in general are very good and give a good idea of what they are intended to represent. Many of them are of special interest in showing the character of syphilitic lesions in the colored race. Taking it all in all this book gives an excellent treatment of syphilis within its limitations of size, and it can be relied upon for an accurate statement of the most essential facts concerning syphilis.

Diathermy. Its Production and Uses in Medicine and Surgery. By ELKIN P. CUMBERBATCH, M.A., B.M. (Oxon.), D. M.R.E. (Camb.), M.R.C.P., Medical Officer in Charge, Electrical Department, St. Bartholomew's Hospital, etc.; Examiner in Medical Electrology, University of Cambridge; Former President, Section of Electrotherapeutics, Royal Society of Medicine. Second edition. 332 pages, 87 illustrations. The C. V. Mosby Company, St. Louis, 1928. Price in cloth, $7.00.

The progress made in recent years in the medical and surgical uses of diathermy, and in the design of apparatus has rendered necessary a complete revision of the first edition and a considerable addition to its size. At the time when that book was written the field of diathermo-therapy had not been widely explored, and it was necessary to advocate much caution in the treatment and to limit the diseases for which it could be safely prescribed. Now, however, the gain of knowledge and experience has confirmed the value of diathermy in the diseases for which it was recommended and established its usefulness in the treatment of other diseases. This has been particularly the case in many of the diseases peculiar to women and in others due to gonococcal infection. The results of the experience gained in the past six years in the Electrical Department of St. Bartholomew's Hospital have been incorporated in the present edition. The parts dealing with the surgical uses of diathermy have been enlarged and almost wholly rewritten, and an introductory account of the new "cutting currents" has been added. The contents of the book include an introduction, historical note, high-frequency currents, the original high frequency generator, the production of currents yielding higher degrees of diathermy, the diathermy machine, the path and distribution of the diathermy current in various conductors, the degree and distribution of heat produced by the diathermy current, the action of diathermy in health, medical diathermy and the use of high-frequency currents in surgery. These chapters discuss very fully the technical side of diathermy and its practical applications in medicine and surgery. It is written simply and sanely, without undue enthusiasm or exaggeration. The general principles and

theory of diathermotherapy can be easily understood and acquired through this book.

Nurses, Patients and Pocketbooks. Report of the Economics of Nursing Conducted by the Committee on the Grading of Nursing Schools. By MAY AYRES BURGESS, Director. 618 pages, 70 tables and 61 diagrams. Published by the Committee, 370 Seventh Avenue, New York, 1928. Price, $2.00.

This is an important economic study made by the Committee on the Grading of Nursing Schools covering its complete findings in its two years study of supply and demand in nursing service. It is founded upon 34,000 returns from nurses, 28,000 returns from physicians, 3,400 returns from hospitals, and 3,200 returns from patients, registrars, etc., in all parts of the country. Dr. William Darrach was the Chairman of this Committee. The data for this book were gathered chiefly through 19 questionnaires, 343,772 of which were sent out, and at the time of publication 67,938 of which had been returned, and additional returns were still being received daily. The text of these questionnaires is contained in the Appendix. The discussion and summary of the important results of this study are beyond the possible limits of a review, and we intend to present these later in an editorial on this subject. Suffice it to say at present that the facts secured have great economic significance to practical medicine, both educational and hospital and private practice. The striking development of the relationship between the nursing profession and the medical profession since 1900 must call for careful thought and consideration by the members of both professions, from the economic aspects alone if from no other. This report should be read by all thoughtful practitioners of medicine.

College News Notes

Dr. Arthur C. Morgan (Fellow), Philadelphia, Pa., and Dr. Thomas G. Simonton (Associate), Pittsburgh, Pa., were speakers at the Seventh Councilor District Meeting of the Medical Society of the State of Pennsylvania at Williamsport on July 13. Dr. Morgan and Dr. Simonton are respectively President and President-Elect of the State Medical Society.

Dr. George F. Pfahler (Fellow), Philadelphia, attended the International Conference on Cancer in London, July 16-22. He also attended the International Congress on Radiology at Stockholm, Sweden, July 23, representing various American radiological societies and the faculty of the Graduate School of Medicine of the University of Pennsylvania.

Dr. Harry Piercy (Fellow), Cleveland, Ohio, served as Secretary and Treasurer of the Western Reserve University Medical Alumni Association from 1919 to 1927 and as President of the same organization from 1927 to 1928; was re-elected President for the ensuing year at the annual meeting of the Association at Cleveland on June 12.

Dr. Oliver T. Osborne (Fellow, and Governor for Connecticut), New Haven, Conn., was recently made an honorary member of the American Medical Editors Association, which Association has recently been organized with Dr. H. Lyons Hunt, New York, as President. Dr. Osborne has been placed on the Committee on Pharmacology and Therapeutics.

Dr. Rollin H. Stevens (Fellow) and Dr. Hans A. Jarre, both of Detroit, Mich., have recently announced the association of Dr. Clyde K. Hasley, former instructor in Dermatology and Roentgenology at the University of Michigan. Drs. Stevens, Jarre and Hasley will limit their practice to X-Ray Diagnosis, Dermatology, Radium and X-Ray Therapy.

Dr. Samuel E. Munson (Fellow), Springfield, Ill., addressed the DeWitt County Medical Society on June 22 on the subject "Cardiac Lesions." Dr. Munson represents the State of Illinois on the Board of Governors of The American College of Physicians.

Dr. E. Bosworth McCready (Fellow), Pittsburgh, Pa., was elected president of the American Therapeutic Society for 1928-29 at the meeting of that Society at Minneapolis, June 9 to 11.

Dr. A. B. Olsen (Fellow), Battle Creek, during the fall of 1927, visited a number of European hospitals and clinics with a special view to observing and studying Epidemic Encephalitis. Last spring he delivered a paper entitled "Some Thoughts on Epidemic Encephalitis Gathered from a Recent Visit to European Hospitals" before the Detroit Neurological and Psychiatric Society, and this paper was later published in full in the Michigan State Medical Society Journal for June.

At the meeting of the American Medical Association at Minneapolis in June, Dr. Olsen read a paper on "The Effect of Liquid Petrolatum Given by Mouth on the Digestion and Absorption of Food."

In the June issue of the American Medical Journal of Surgery, Dr. Olsen, in collaboration with Dr. James T. Case, published an article on "Circumscribed False Peripheral Neuromata."

Dr. Wm. E. Gardner (Fellow), Louisville, Ky., who is Chairman of the Section on Neurology and Psychiatry of the Southern Medical Association, in his an-

nual address to the Section at Asheville, N. C., November 12 to 15, will discuss "A Decade of Transition in American Psychiatry."

Dr. John F. Kenney (Associate), Pawtucket, R. I., was recently appointed Consulting Physician to the new Providence Lying In Hospital of Providence, Rhode Island, also Associate Physician at St. Josephs Hospital of Providence and reappointed Consulting Physician to the Sturdy Memorial Hospital of Attleboro, Mass.

Dr. H. Lisser (Fellow), San Francisco, Calif., is Associate Clinical Professor of Medicine at the University of California Medical School, and Chief of the Ductless Gland Clinic. Dr. Lisser delivered the Presidential address before the Twelfth Annual Scientific Session of The Association for the Study of Internal Secretions at Minneapolis, June 12, 1928, entitled, "Uni-Glandular Origin of Pluri-Glandular Syndromes, as Illustrated by Disturbances of Menstruation." He is author of the section on "Diseases of the Ductless Glands," Blumer's System of Bedside Diagnosis, published by Saunders and Company, 1928, Third Volume: also author, with Dr. George Dock (Fellow), Pasadena, chapters on "Diseases of the Ductless Glands," Osler and McCrae "Modern Medicine," Volume 5, 1928. Dr. Lisser is also Associate Clinical Editor of "Endocrinology," the official publication of the Association for the Study of Internal Secretions.

Dr. E. Roland Snader, Jr., (Fellow) and Mrs. Snader, Philadelphia, are receiving congratulations on the birth of a son, Edward Roland Snader, 3rd, on July 3.

Dr. and Mrs. Carl V. Vischer, Philadelphia, and their son Carl V. Vischer, 3rd, and daughter Jean Frances Vischer sailed on August 1 on a Canadian cruise to Halifax, Quebec and the Saguenay.

Dr. Fred C. Oldenburg (Fellow), Cleveland, has been promoted to Senior Clinical Instructor in Medicine at Western Reserve Medical College. Dr. Oldenburg was also elected Secretary-Treasurer of the Western Reserve Medical Alumni Association.

Dr. Edward Matzger (Associate), San Francisco, recently received the following appointments: Chief of Asthma and Hay Fever Clinic, San Francisco Polyclinic Hospital; Associate in Research, Hooper Foundation, University of California; Consultant Immunologist, Southern Pacific General Hospital, San Francisco, Calif.

Dr. Matzger is the author of "A Common Sense Viewpoint of the Significance of Skin Tests" and "A Summary to Date of the Technic of Local Passive Transfer," appearing in the May and June numbers, respectively, of California and Western Medicine.

Dr. Joseph M. King (Fellow), Los Angeles, Calif., is a member of the Educational Committee of the new medical school to be opened this fall by the University of Southern California at Los Angeles.

Dr. James G. Carr, Jr. (Fellow), Chicago, Ill., has been elected President of the Cook County Hospital Interns' Alumni Association.

Dr. Ada E. Schweitzer (Fellow), Indianapolis, Ind., addressed the Rush County Medical Society on June 12, on health work among school children. Dr. Schweitzer is Director of Child Hygiene of the Indiana Board of Health.

Dr. Rutherford B. H. Gradwohl (Associate), St. Louis, Mo., Lt. Col., U. S. Naval Reserve, was on duty with the U. S. Fleet in Hawaiian waters from April 12 to May 20 of the past spring.

Dr. Joseph W. Larimore (Fellow), St. Louis, Mo., has been promoted to Assistant Professor of Medicine at the Washington University Medical School.

Dr. Estella G. Norman (Fellow), Battle Creek, Mich., has been appointed by Governor Fred Green as a member of the Michigan Board of Registration of Nurses and Trained Attendants. The law requires that

this Board consist of the State Health Commissioner, one other physician and three registered nurses, the latter usually being superintendents of nurses' training schools.

Dr. Harold C. Bean (Fellow), Portland, Oregon, spoke before the Central Willamette Medical Society on June 7, at Eugene, on the subject "Diagnostic Problems in Internal Medicine."

Dr. Walter C. Alvarez (Fellow), Rochester, Minn., addressed the Sixth and Eighth Councilor District Medical Societies of Wisconsin, June 11, on "How to Diagnose Gastro-Intestinal Disease from a Good History."

Dr. Isidore S. Kahn (Fellow), San Antonio, Texas, addressed the Milwaukee, Wisconsin, Oto-Ophthalmic Society, June 8, on "Bronchial Asthma."

Dr. Ralph C. Matson (Fellow), Portland, Oregon, was elected Vice-President of the American Sanatorium Association at its twenty-third annual meeting in Portland in June.

Dr. Joseph C. Doane (Fellow), Philadelphia, Pa., officiated as President at the annual convention of the American Hospital Association, held in San Francisco, August 6 to 10.

Dr. Preston M. Hickey (Fellow), Ann Arbor, Mich., delivered the Caldwell lecture at the twenty-ninth annual meeting of the American Roentgen Ray Society at Kansas City, Mo., September 25 to 28. Dr. Hickey is Professor of Roentgenology at the University of Michigan Medical School.

Dr. Julian R. Blackman (Fellow), of the U. S. Veterans' Bureau, has received an appointment at Palo Alto, Calif. Dr. Blackman was formerly Radiologist at the Immanuel Hospital and the U. S. Veterans' Bureau at Omaha, Nebr.

OBITUARY

Dr. Joseph Bieber, New York, N. Y. (Fellow, February 24, 1926), died May 16, 1928, of Coronary Embolus and Pulmonary Infarct; aged 50. Dr. Bieber was graduated from the College of Physicians and Surgeons of Columbia University in 1900 and, since 1911, had been attending physician at the People's Hospital. He was a member of the Medical Society of the County of New York, the New York State Medical Society and a Fellow of the American Medical Association.

NEW HOME FOR THE COLLEGE

On October 1, the Executive Offices of The College will be moved from the Covington Hotel in Philadelphia to their permanent new quarters at 133-135 South 36th Street, Philadelphia, which is a newly constructed building used almost exclusively for professional offices. The headquarters at the Covington Hotel were purely temporary, awaiting the time when a suitable location could be secured permanently.

In the new building there will be ample space for conducting the work and keeping The College records. The location faces the campus of the University of Pennsylvania and is in a dignified and educational atmosphere. It is readily accessible (only three squares) from the West Philadelphia station of the Pennsylvania Railroad.

The headquarters were selected by a subcommittee of The College, and fulfill an urgent need for a permanent College home. The Executive Secretary, Mr. Loveland, will be especially pleased to have members of The College stop at the headquarters whenever opportunity permits.

VOLUME FILE FOR ANNALS

The Executive Secretary of The College has had manufactured a suitable volume file for Annals of Internal Medicine. This file is in the form of a two section box file, made of durable material and suitable in size to contain one complete volume of Annals. It is indexed on the front and may be conveniently placed on the book-shelf where each volume of the Journal may be preserved and where it will be readily accessible for reference. The cost, prepaid, is $1.25.